National Institute for Health and Care Excellence

Bipolar disorder (update)

Guideline Consultation Table

17 April - 29 May 2014

Stakeholder	Order No	Document	Section No	Page No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
British Association for Behavioural and Cognitive Psychotherapies	1	NICE	General	General	There is repeated reference throughout to recommending the use of "manualised" psychological interventions. However, it's not clear from this guideline what this would include. I guess any therapy could have a manual. The term is used as if it's an indication of quality.	Thank you for your comment; the term 'manualised' has been replaced with the description 'with a published manual describing how it should be delivered'. In addition, a footnote has been added specifying that a manual should be: *"defined as being based on at least one randomised controlled trial published in a peer review journal showing effectiveness in on depression symptoms in bipolar depression or in long-term treatment to reduce relapse in people with bipolar disorder."*
British Association for Behavioural and Cognitive Psychotherapies	2	NICE	General	General	It is excellent to see repeated reference to the need to involve carers where possible. However, there is no guidance for clinicians about what can be offered to carers when the service user does not wish to have them involved, and yet they are still responsible for their wellbeing / living with them.	Thank you for your comment. The guideline has made a recommendation that the clinical team does provide information to carers when they have a direct responsibility for looking after the service user irrespective of the service user's willingness for them to talk to the clinical team.
British Association for Behavioural and Cognitive Psychotherapies	3	Full	2.6.4	48	I think one of the references is wrong – Johnson et al 2011 I think should the Jones et al reference above in the reference list?	Thank you for your comment, this has been amended.
British Association for Behavioural and Cognitive Psychotherapies	4	Full	9	General	In this section it seems that consideration has not been given to the impact of lifestyle interventions (particularly exercise) upon mental health, in terms of potential both for benefit and for harm. There has been relatively little empirical investigation of this area, however I believe this issue merits mention because of	Thank you for your comment. The GDG found no specific evidence on exercise to make a recommendation in bipolar disorder. Other research recommendations were considered to have a higher priority.

					a) the evidence base for beneficial effects of exercise upon mental health in unipolar depression; b) the theoretical risk of iatrogenic effects of exercise during hypomania / mania (see Wright, Armstrong, Taylor & Dean, 2012); c) the potential for the guideline to make research recommendations if suitable empirical investigation is absent.	
British Association for Behavioural and Cognitive Psychotherapies	5	NICE FULL	1.2.5, 1.6.1, 1.11.12	10, 20 11, 26-7 14, 42 148, 256,	The recommendations for the use of psychological treatments recommended in the (unipolar) depression guidance contradicts the statement in the FULL guideline (p48, lines 5-6) that "the treatment offered is likely to be generic and lacks an evidence base for this condition" The argument in the FULL guidance (p256) that the quality of evidence for unipolar psychological interventions is higher than for bipolar does not (in our view) justify the assumption that unipolar interventions are safe and effective for a bipolar population - this would require additional evidence that interventions for one condition could be applied to another condition. Indeed this assumption runs counter to theoretical models that suggest mania may be triggered by actions intended to avoid depression - e.g. Abraham, 1911, Neale, 1988; Lyon et al, 1999; Mansell et al, 2007) We agree with the recommendation that psychological interventions should be conducted by psychological therapists who have training and expertise in working with people with bipolar disorder". Such therapists should to be able to deliver evidence-based bipolar-specific psychological treatments, so it is unclear why these therapists would opt to provide generic/unipolar interventions instead. Also, the potential risk that depression-focused interventions (e.g. behavioural activation) may trigger mania or hypomania requires careful consideration..	Thank you for your comment. The sentence on page 48 relating to 'lack of an evidence base' has been removed because it was misleading. The GDG noted that the evidence for psychological interventions for unipolar depression is consistent with the evidence for bipolar depression and of much higher quality, and therefore the use of interventions for unipolar were deemed appropriate for this population.
British Association for Behavioural and Cognitive Psychotherapies	6	NICE	1.7.3	12	We support this recommendation for the use of bipolar-specific psychological interventions to prevent/reduce relapse risk and address residual difficulties.	Thank you for your comment.

British Association for Behavioural and Cognitive Psychotherapies	7	NICE FULL	1.3.1, 1.3.5	22, 23 224	Whilst Early Intervention services are well placed to support a normalising, recovery focused and youth-friendly assessment of people with a suspected first episode, there are likely to be resource implications for EI services that are typically only funded to work with caseloads based on population estimates of the incidence of psychoses, so accepting all cases of suspected bipolar (including bipolar 2 and bipolar 1 without psychotic features) is likely to require changes to commissioning arrangements as well as service entry criteria to respond to increased demand. Early Intervention services are commissioned to accept referrals from people aged 14-35, so they would not be appropriate for people who require assessment and treatment but are outside of these age parameters (whether because of late onset or long duration of unrecognised/undiagnosed bipolar symptoms).	Thank you for your comment. The psychosis and schizophrenia guideline looked at the evidence underpinning the use of EIS services for people with suspected and early psychosis. These populations include people who later develop schizophrenia, bipolar disorder and other psychoses. All the trials included were with mixed populations. We accept that schizophrenia and bipolar are different conditions, with different guidelines. However, there is considerable overlap in the treatment and management of these conditions. It is also important that, for both groups access to a service that works on the principle of early intervention is important. The GDG does however concede that there is some variation in service provision, and has therefore revised the recommendation to set out the components of the teams that should provide assessment for bipolar disorder, rather than stating that the team must be EIS. Recommendation 1.3.5 has been merged with revised recommendation 1.3.1.
British Association for Behavioural and Cognitive Psychotherapies	8	NICE	1.7.1	29-30	The recommended content of discussion appears very medically focused and could be substantially improved by being a) based on individual needs, b) recovery focused (ie optimistic & empowering, paying attention to wellbeing and psychosocial functioning rather than simply symptom management and relapse prevention), c) decatastrophising (in light of the theoretical possibility that mood instability may be exacerbated by fear of relapse, cf Mansell et al, 2007).	Thank you for your comment. The Guideline Development Group agrees that a focus on recovery is important, and endeavoured in its guideline to capture this as far as the evidence would allow. Recovery is given some prominence in the recommendations about carers (revised recommendations 1.1.14, 1.1.18) and primary care (1.2.4), and the section on 'Promoting recovery and return to primary care' sets out the service context. In response to your comment, the GDG has, in addition, strengthened the first recommendation in the guideline to emphasis recovery and building relationships, and added the importance of personal recovery goals to revised recommendation 1.3.2.
British Association	9	NICE	1.7.2 -	30-31	We support these recommendations although most	Thank you. The recommendations do say

for Behavioural and Cognitive Psychotherapies			1.7.4		healthcare providers are likely to struggle to meet demand if such interventions are offered to all people with bipolar disorder. In order to maximise the likelihood that providers will work towards increasing capacity to deliver these interventions, it would be helpful if the recommendations stated unequivocally that they should be offered to all service users (or all families/carers where applicable).	offer people with bipolar. The GDG did not see the need to add in all people as there are no exceptions in the recommendations.
British Association for Behavioural and Cognitive Psychotherapies	10	FULL NICE	General	32	Whilst the FULL guideline acknowledges the literature on trauma (and particularly childhood trauma) in the lives of many people with bipolar disorder, we were unable to find any recommendations in the NICE guidance on a) assessment and formulation of the potential role of trauma in making sense of bipolar presentations (including assessing current risks, as well as safeguarding), b) treatment recommendations (even if simply a reference to the PTSD guidance), and c) research recommendations (e.g. development and evaluation of psychological interventions for comorbid PTSD and bipolar).	Thank you for your comments. Revised recommendation 1.3.2 on the assessment of people with suspected bipolar disorder makes reference to the consideration of psychosocial factors with reference to both current mood and past episodes. We would expect secondary care mental health professionals to be aware that trauma may a relevant factor to consider. However, we have received a number of comments that asked us to consider developmental issues over the lifespan which has been added to revised recommendation 1.3.2. These might include trauma as well as other issues. The issue of safeguarding is covered in revised recommendation 1.1.19. It is not possible to make recommendations in every clinical scenario. There are also only a limited number of research recommendations that can be made and the GDG considered other recommendations to have greater priority.
British Association for Behavioural and Cognitive Psychotherapies	11	NICE FULL	1.2.5, 1.6.1, 1.11.12	10, 20 11, 26-7 14, 42 148, 256,	The recommendations for the use of psychological treatments recommended in the (unipolar) depression guidance contradicts the statement in the FULL guideline (p48, lines 5-6) that "the treatment offered is likely to be generic and lacks an evidence base for this condition" The argument in the FULL guidance (p256) that the quality of evidence for unipolar psychological interventions is higher than for bipolar does not (in our view) justify the assumption that unipolar interventions are safe and effective for a bipolar population - this would require additional	Thank you for your comment. The sentence on page 148 relating to 'lack of an evidence base' has been removed because it was misleading. The GDG noted that the evidence for psychological interventions for unipolar depression is consistent with the evidence for bipolar depression and of much higher quality, and therefore the use of interventions for unipolar were deemed appropriate for this population.

					evidence that interventions for one condition could be applied to another condition. Indeed this assumption runs counter to theoretical models that suggest mania may be triggered by actions intended to avoid depression - e.g. Abraham, 1911, Neale, 1988; Lyon et al, 1999; Mansell et al, 2007) We agree with the recommendation that psychological interventions should be conducted by psychological therapists who have training and expertise in working with people with bipolar disorder". Such therapists should to be able to deliver evidence-based bipolar-specific psychological treatments, so it is unclear why these therapists would opt to provide generic/unipolar interventions instead. Also, the potential risk that depression-focused interventions (e.g. behavioural activation) may trigger mania or hypomania requires careful consideration..	
British Association for Behavioural and Cognitive Psychotherapies	12	NICE	1.7.3	12	We support this recommendation for the use of bipolar-specific psychological interventions to prevent/reduce relapse risk and address residual difficulties.	Thank you.
British Association for Behavioural and Cognitive Psychotherapies	13	NICE FULL	1.3.1, 1.3.5	22, 23 224	Whilst Early Intervention services are well placed to support a normalising, recovery focused and youth-friendly assessment of people with a suspected first episode, there are likely to be resource implications for EI services that are typically only funded to work with caseloads based on population estimates of the incidence of psychoses, so accepting all cases of suspected bipolar (including bipolar 2 and bipolar 1 without psychotic features) is likely to require changes to commissioning arrangements as well as service entry criteria to respond to increased demand. Early Intervention services are commissioned to accept referrals from people aged 14-35, so they would not be appropriate for people who require assessment and treatment but are outside of these age parameters (whether because of late onset or long duration of unrecognised/undiagnosed bipolar symptoms).	Thank you for your comment. The psychosis and schizophrenia guideline looked at the evidence underpinning the use of EIS services for people with suspected and early psychosis. These populations include people who later develop schizophrenia, bipolar disorder and other psychoses. All the trials included were with mixed populations. We accept that schizophrenia and bipolar are different conditions, with different guidelines. However, there is considerable overlap in the treatment and management of these conditions. It is also important that, for both groups access to a service that works on the principle of early intervention is important. The GDG does however concede that there is some variation in service provision, and has therefore revised the recommendation to set

						out the components of the teams that should provide assessment for bipolar disorder, rather than stating that the team must be EIS. Recommendation 1.3.5 has been merged with revised recommendation 1.3.1.
British Association for Behavioural and Cognitive Psychotherapies	14	NICE	1.7.1	29-30	The recommended content of discussion appears very medically focused and could be substantially improved by being a) based on individual needs, b) recovery focused (ie optimistic & empowering, paying attention to wellbeing and psychosocial functioning rather than simply symptom management and relapse prevention), c) decatastrophising (in light of the theoretical possibility that mood instability may be exacerbated by fear of relapse, cf Mansell et al, 2007).	Thank you for your comment. The Guideline Development Group agrees that a focus on recovery is important, and endeavoured in its guideline to capture this as far as the evidence would allow. Recovery is given some prominence in the recommendations about carers (revised recommendations 1.1.14, 1.1.18) and primary care (1.2.4), and the section on 'Promoting recovery and return to primary care' sets out the service context. In response to your comment, the GDG has, in addition, strengthened the first recommendation in the guideline to emphasis recovery and building relationships, and added the importance of personal recovery goals to revised recommendation 1.3.2.
Bipolar UK	1	Full	2.2.6	32	Suggest you include additional antecedent factors, e.g. health trauma, brain injury, to highlight not always child maltreatment.	Thank you for your comment. There is a long list of potential aetiological factors that might operate in a small number of cases and there is not scope in an introduction to list them all. On the other hand childhood maltreatment is common unfortunately so it has been specifically considered.
Bipolar UK	2	Full	2.6.1	43	Highlights the need for GPs and medical professionals to engage and work with that national bipolar charity (Bipolar UK) who is facing unprecedented service demand.	Thank you for your comment. NICE does not usually make a specific recommendation for people to work with any named third sector or commercial organisation.
Bipolar UK	3	Full	2.6.2	45	Tier 4 admission should also be considered for complex presentations where diagnosis is unclear	Thank you for your comment. The GDG did not wish to specify that admission should be used to diagnose complex presentations because there are many considerations in relation to hospital admission. Such decisions should rest with tier 4 services.
Bipolar UK	4	Full	2.7	53	The majority of the studies referenced focus on the costs of bipolar but this summary paragraph uses the	Thank you for your comment. Burden would indeed be used in this context in relation to any

					term “burden” in lines 14 and 21. A number of our service users queried would burden be used if talking about a severe physical illness. In their view likely not.	health problem whether physical or mental e.g. the World Health Organisation Global Burden of Disease study.
Bipolar UK	5	Full	3.5.2	60 61	Drafting re sensitivity and specificity is well explained and very clear	Thank you for your comment.
Bipolar UK	6	Full	3.5.2	61 (to 63)	Explanation focusing on receiver operator characteristic curves and forest plots could perhaps be redrafted with greater clarity.	Thank you for this suggestion, but this text has been used for many guidelines and there have not been any comments suggesting it needs clarifying. However, we’ve reviewed it again, and removed the use of unnecessary abbreviations.
Bipolar UK	7	Full	4		Greater clarification should be given to the interpretation of carers as many of our service users do not recognize this term. They are families/loved ones of an individual with bipolar but not always a carer. We suggest at the outset you refer to carers as including families and loved ones.	Thank you for your comment. A definition of carers has been added to the start of chapter 4.
Bipolar UK	8	Full	4.0.1	78	There is an end bracket missing after “schizophrenia”	Thank you, this has been corrected.
Bipolar UK	9	Full	1.1.5.6 1.1.18	83	As highlighted in 7, the current wording has the unintended impact of excluding those who are not regarded as official carers. For example it would be helpful to include a guideline for an individual to nominate another named person.	Thank you for your comment. The term ‘carer’ also applies to anyone who carers for another person in an informal unpaid capacity. This has been added to the definition at the start of the guideline.
Bipolar UK	10	NICE/Full	1.1.17/ 4.4.1.6		This should be reviewed regularly as is often the case an individual may refuse to name another carer/individual when unwell but will reconsider when more stable.	Thank you for your comment, the previous recommendation (1.1.16) states that the person’s preference for communicating with carers should be regularly reviewed.
Bipolar UK	11	Full	5.1	92	In 2012 the Royal College of Psychiatrists, Bipolar UK and Bipolar Scotland completed a survey to the challenges of diagnosis. The need for a consistent screening tool was one of the major priorities highlighted by medical professionals.	Unfortunately, the evidence review did not support a specific ‘screening tool’ or questionnaire, hence we don’t recommend this. Instead, we have advised that professionals refer for any severe presentation, and consider referral for assessment if there are suggestions of elevated mood in people presenting with less severe depressions. It is worth noting that 10% of people who develop depression in primary care will turn out to have bipolar disorder.
Bipolar UK	12	Full	5.3.3	100	It is often difficult for individuals (particularly those newly diagnosed) to identify their triggers. It would	Thank you for your comment. Mood diaries and scales are indeed tools that health

					help immensely if patients were encouraged and indeed handed information about completing mood diaries/scales to help them better understand their mood cycles.	professionals should consider. However, they are not appropriate or suitable in every person with suspected bipolar disorder so the GDG has decided not to require them in every assessment.
Bipolar UK	13	NICE/Full	1.2.1/ 5.6.1.1	107	This question relies on self disclosure and when severely depressed individuals may not be self-aware. Again reference and use of mood diaries/scales would assist both primary professionals and patients.	Thank you for your comment. Mood diaries and scales are indeed tools that health professionals should consider. However, they are not appropriate or suitable in every person with suspected bipolar disorder so the GDG has decided not to require them in every assessment.
Bipolar UK	14	NICE/Full	1.11.7/5 .6.1.24	110	The guidelines state 'Do not diagnose Bipolar II disorder in children and young people'. There is concern re diagnosis of hypomania in youth but this is perhaps too strongly worded.	Thank you for your comment. This recommendation has been removed and the 'evidence to recommendations' section in the full guideline has been amended.
Bipolar UK	15	Full	10.1	273	Further clarity on the status of lithium would be helpful – the SPC states that it is not recommended in under 12s, implying that it can be prescribed in those 12 and over.	Thank you for your comment. This is an unusually difficult area, depending upon the brand of lithium used. Priadel tablets, Priadel liquid, Li-Liquid and Camcolit tablets are only licensed for 18 years upward. The only preparation that does have a license from age 12 upwards is Liskonum tablets. The BNFc lists Camcolit as well as Liskonum as options in 12 years and above despite only one of them being licensed. It is not clear why Camcolit is listed as an option for children, but the manufacturer of Camcolit has previously confirmed that it is definitely *not* licensed in this age group. The manufacturer was unsure why the BNF has not indicated the fact that it is not licensed as there is usually a statement to that effect when they include drugs without licenses. The statement has therefore been modified to say that *some* preparations of lithium are licensed for use in those over 12 years.
Bipolar UK	16	Full	10.1	274	It should be noted that this guidance is out of date, is currently being reviewed and recent Cochrane meta-analyses provide a more up-to-date review of the	We accept the view expressed, however, this is the guidance currently in practice. Reference is now made to the more up-to-date Cochrane

					evidence for treatment (eg Cox; Hetrick 2012)	review (Hetrick et al., 2012).
Bipolar UK	17	Full	10.1	274	The statement on fish oils could be more circumspect – it implies effectiveness in a range of disorders.	Thank you for your comment, we agree and the statement has been modified, omitting reference to wider use.
Bipolar UK	18	Full	10.7.2	293	Although it is important to minimise use of AAPs due to adverse effects, the statement that they can only be used for 12 weeks is extremely concerning. This does not take into consideration the relatively rare but very serious, high risk cases of adolescent BP that are admitted to inpatient units, who are often difficult to treat. These YP often need trials of different AAPs in order to establish the best risk/benefit profile for each YP. They may also have chronic relapsing conditions, and each relapse may be associated with high risk suicide attempts and other risks such as vulnerability to sexual exploitation. In these cases the benefits of longer-term medication often outweighs the risks. Even within this draft , the expert opinion is quoted from the aripiprazole appraisal (pg 283) which states that the average duration of AAP treatment in YP can reach 12 months (and in rare cases possibly longer). Thus these recommendations ignore this expert opinion and also discriminate against young people with a serious disorder. In addition, this time limit is not stipulated in the psychosis guidelines, hence this draft is at odds with other expert opinion. Research also suggests that affective disorder is a leading cause of suicide in YP and that these cases are undertreated (Windfuhr JCPP 2008).	Thank you for your comment. The recommendation on aripiprazole comes from the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be “routinely” continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
Bipolar UK	19	Full	10.7.2	294	The statement that there is no evidence of long-term benefit is based on the fact that there is very little available evidence base; this does not necessarily mean that some YP may not benefit from longer term treatment. The draft acknowledges that there may be some YP who may benefit from longer term treatment (‘most’ not ‘all’ is used in line 21), but then goes on to categorically state that long-term treatment should not be used. In light of the comments above, it would be helpful if this statement could be re-considered.	Thank you for your comment. The GDG still do not believe that pharmacological interventions should be used for the long-term management of bipolar disorder in children and young people based on the current evidence base. The recommendation on aripiprazole comes from the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young

						people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be “routinely” continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
Bipolar UK	20	Full	10.7.5	295	Again, this draft is incongruent with the guidance on psychosis which states that there is a high risk of relapse if AAPs are stopped within 1-2 years of an episode. This sends a very confusing and contradictory message to clinicians and service users: if there is a BP episode with psychosis, then AAPs can be used for up to 2 yrs but only for 12 weeks without psychosis, although the risk of adverse effects is the same.	Thank you for your comment. The GDG recognised the growing evidence of harms associated with antipsychotics, especially those in most common use at the time of writing (olanzapine, quetiapine etc) which are strongly associated with metabolic syndromes such as diabetes. However, given the lack of evidence regarding the efficacy of <u>any</u> pharmacological treatment of bipolar disorder in children and young people, the GDG therefore decided to extrapolate from the adult data, which prioritises antipsychotics over lithium and valproate for acute mania. Because bipolar disorder is a relapsing and remitting condition that rarely becomes chronic, the use of antipsychotics is bound to be needed for shorter amounts of time than in people with schizophrenia where psychotic episodes are longer and become chronic. The only drug licenced is aripiprazole, which is the subject of a technology appraisal, and both the licence and the TA limit the use of aripiprazole to 12 weeks. However, we do take your point that sometimes antipsychotics are needed for longer than 12 weeks, and have therefore amended the recommendation to say that drug treatment should not ‘routinely’ continue for longer than 12 weeks, and that at 12 weeks there should be a multidisciplinary review to assess whether to continue treatment.
Bipolar UK	21	NICE/Full	1.11.10/	296	See above:	Thank you for your comment. There is very

			10.8.1.3		Again, this draft is incongruent with the guidance on psychosis which states that there is a high risk of relapse if AAPs are stopped within 1-2 years of an episode. This sends a very confusing and contradictory message to clinicians and service users: if there is a BP episode with psychosis, then AAPs can be used for up to 2 yrs but only for 12 weeks without psychosis, although the risk of adverse effects is the same.	little evidence regarding the efficacy of any antipsychotic treatment of bipolar disorder in children and young people. However, there is growing evidence of the harms associated with the antipsychotics, especially those in most common use at the time of writing (olanzapine, quetiapine etc) which are strongly associated with metabolic syndromes such as diabetes. Because bipolar disorder is a relapsing and remitting condition that rarely becomes chronic, the use of antipsychotics is bound to be needed for shorter amounts of time than in people with schizophrenia where psychotic episodes are longer and become chronic. The only drug licenced is aripiprazole, which is the subject of a technology appraisal, and both the licence and the TA limit the use of aripiprazole to 12 weeks. However, we do take your point that sometimes antipsychotics are needed for longer than 12 weeks, and have therefore amended the recommendation by adding the word 'routinely'.
Bipolar UK	22	Full	1.11.15/ 10.8.1.8	296	This recommendation takes no consideration of levels of severity and ability to engage with psychological treatment; in severe high risk cases of depression often YP struggle to engage in psychological treatment and may need a pharmacological intervention much sooner than after several months of attempted psychological treatment. Further there is no evidence currently demonstrating the efficacy of CBT in managing bipolar depression	Thank you for your comment. Severity and the considerations to be taken into account when prescribing medication is directly addressed in recommendation 1.11.15. The Guideline Development Group believes the wording in recommendations 1.11.12 and 13 was misleading therefore it has been clarified. The intention was not to suggest that medication should not be considered until after 3 months of psychological therapy. The group thinks the confusion may have arisen because it states 4 to 6 *sessions* rather than 4 to 6 *weeks*. This has been rectified. The Guideline Development Group agrees that risk needs to be considered and have therefore added a recommendation to take this into account.

						There is very little evidence for the treatment of bipolar disorder in children and young people – for pharmacological *or* psychological interventions. The GDG therefore extrapolated from the evidence in adults, please see section 10.7 in the full guideline for the rationale for this method.
Bipolar UK	23	NICE/Full	1.11.11/ 10.8.1.4	296	Although caution is required, there may be exceptionally severe cases which require combination treatment with an AAP. YP often refuse Li as an option due to blood monitoring, and in these cases the risks of using valproate need to be discussed with the adolescent girl and carer and an informed choice made. Although US guidelines caution against valproate it is not contra-indicated.	Thank you. Although there may be occasions when two antipsychotics may be used, such as during changeover from one antipsychotic to another, taking two has no basis in evidence. Also, valproate has a high incidence of congenital malformations and shouldn't be used for girls or women of childbearing potential.
British Association for Psychopharmacology	1	NICE	General	General	It is good to see a revised version of the 2006 Guideline as the evidence base has increased markedly since then. There are many good aspects of the new guideline but there are some issues that would benefit from clarifying or amending as listed these below.	Thank you for your comments.
British Association for Psychopharmacology	2	General (both)	General	General	Many patients will not respond to all listed options and BPD is a complex and difficult condition to manage. We recommend the guidelines include a statement about offering all patients a second opinion (in line with other NICE guidelines) and offering non-responsive patients referral to tertiary level services with specialist expertise in the treatment of refractory bipolar disorder. There is some evidence supporting this (eg: Kessing et al. 2013 B J Psych).	Thank you for your comment, this guideline is to be read alongside the service user experience in adult mental health guideline (NICE CG 136, recommendation 1.3.4), which includes access to a second opinion. Tertiary level services were outside the scope of this guideline.
British Association for Psychopharmacology	3	NICE	General	General	BPD is one of the most comorbid psychiatric disorders with particularly high rates or comorbid anxiety disorders and substance misuse. Some further comments on the importance and management of comorbidity would be helpful.	Thank you for your comments. The section at the start of the guideline – "Treatment and support for specific populations" – refers professionals to the guidelines for conditions which are commonly comorbid with Bipolar Disorder. These include borderline and antisocial personality disorders, generalised anxiety disorder, substance misuse problems, problems experienced around birth for the

						mother, people with a learning disability and the aging population.
British Association for Psychopharmacology	4	NICE	1.6.1	12	For consistency we recommend adding to psychological interventions: “Discuss with the person the possible benefits and risks for this intervention”	Thank you for your comment, with which the Guideline Development Group agrees. The sentence you have suggested has been added to the recommendation.
British Association for Psychopharmacology	5	NICE	General	General	A practical issue is that many patients seen in the NHS do not have English as a first language. The evidence that psychological interventions are effective in patients in whom English is not a first language should be considered.	Thank you for your comments. The guideline recommends that professionals working with children and young people with bipolar disorder should heed the recommendations in the general principles of care in the psychosis and schizophrenia guideline, which includes a substantial section on ethnicity, minorities and therapy with non-English speaking people. A recommendation has been added to also reference the relevant section on race, culture and ethnicity from the psychosis and schizophrenia in adults’ guideline, which also addresses these issues.
British Association for Psychopharmacology	6	NICE	1.1.6	16	While the management of comorbidities was outwith the scope of the GDG, simple reference to other NICE guidelines with regards to the management of, for example, anxiety in the context of bipolar disorder appears weak and potentially misleading. First line pharmacological options for the management of GAD include SSRIs. Given the data show lack of efficacy of SSRIs in bipolar disorder and the concern that antidepressants may destabilise the disorder, this is a concern. At the very least there needs to be a caveat added to section 1.1.6	Thank you for your comment. The GDG found very little specific evidence for or against specific treatments for anxiety disorders in bipolar disorder. In such circumstances it is usual for NICE to recommendation consideration of existing NICE guidelines for the management of comorbid conditions. The GDG has however added that clinicians need to use their clinical judgement and be alert to the potential for drug interactions when treating comorbidities. Additionally, the section at the start of the guideline – “Treatment and support for specific populations” – refers professionals to the guidelines for conditions which are commonly comorbid with Bipolar Disorder. These include borderline and antisocial personality disorders, generalised anxiety disorder, substance

						misuse problems, problems experienced around birth for the mother, people with a learning disability and the aging population.
British Association for Psychopharmacology	7	NICE	1.2.5	20	The evidence base for CBT either to treat bipolar depression or prevent its recurrence is not as strong as is suggested, eg: in the prevention of bipolar recurrence the largest RCT to date by Scott J et al (Br J Psych. 2006; 188:313-20) showed no effect of CBT versus treatment as usual. In addition caveats are needed before extrapolating from the much stronger and supportive evidence base for using CBT in unipolar depression to bipolar depression. There is increasing evidence that the two forms of depression are distinct.	Thank you for raising this issue. The GDG discussed this again, but decided not to change 'offer' to 'consider' in recommendations 1.2.5 and 1.6.1. In doing so, they took into account the totality of evidence and came to the consensus that at present there is insufficient evidence to conclude that the two forms of depression are distinct. Therefore, they thought that a stronger recommendation was warranted. Please also note that we have amended recommendation 1.6.1 (NICE guideline) to make it clear that the healthcare professional should discuss with the person with bipolar disorder the possible benefits and risks of psychological interventions and monitor mood carefully for signs of mania or hypomania or deterioration of the depression symptoms. In addition, recommendation 1.6.2 makes it clear that psychological therapists working with people with bipolar depression should have training in, and experience of, working with people with bipolar disorder.
British Association for Psychopharmacology	8	NICE	1.2.5	20	Notwithstanding the comments above, at a pragmatic level many primary care services (eg IAPTS) routinely exclude all bipolar patients (bipolar 1 and 2) with the result that patients with mild or moderate BP depression cannot access treatment in primary care but will often not meet the threshold to access secondary services. As a result such bipolar patients are often untreated. This is a major clinical problem. Some comment from NICE about the appropriateness of minor/moderate depressive episodes in BP 1 and 2 disorder (without major risk) being managed in primary care would be helpful to patients.	Thank you for your comment. We agree that people with bipolar disorder should not be excluded from psychological treatment and a likely provider of such treatment would be IAPT. Hence, the recommendation that people with bipolar depression should receive psychological treatment is a key recommendation. However, NICE does not usually name a specific provider of such services. It has specified that such treatment should be delivered by health professionals with experience of bipolar disorder and also that the severity of depression must be considered.

British Association for Psychopharmacology	9	NICE	1.2.12	21	Please add thyroid function for lithium	Thank you for your comment, monitoring thyroid function has been added to the recommendation.
British Association for Psychopharmacology	10	NICE	1.3.5	23	There is a lack of evidence to support the contention that bipolar disorder should be managed in EIP services for the first 3 years and we question the ability of many EIP services to do this except in the case of a patient presenting with mania or a psychotic episode for the following reasons. First, and most important, it is not clear that most EI services have the knowledge or skills to do this as their training is geared to assessing and managing prodromal schizophrenia and early psychosis (something these teams do extremely well). If EI teams are to take on BPD then it will require a major investment and retaining. Second most patients with BPD don't have psychotic symptoms when acutely ill and most EI services have 'psychosis' as an entry criteria. Finally, there is an absence of evidence that the outcome for BPD in UK EI teams is superior to the outcome for such patients treated in CMHTs.	Thank you for your comment. EIS, as you say, deal with prodromal and actual psychosis. These two categories will include people later diagnosed with bipolar disorder. If a person has only been depressed but not psychotic, they will be treated in IAPT of in a CMHT. If they then develop a psychosis or hypomania, they are best placed in a team that can deal with this – an EIS team. The outcome for people with psychosis in EIS is well established. The trials include people who later are found to have bipolar and schizophrenia. The outcomes for both are better than for standard care. The GDG does however concede that there is some variation in service provision, and has therefore revised the recommendation to set out the components of the teams that should provide assessment for bipolar disorder, rather than stating that the team must be EIS. Please note, recommendation 1.3.5 has been merged with revised recommendation 1.3.1.
British Association for Psychopharmacology	11	Full	6.2 & 6.5		NICE guideline: section 1.5.3 page 15 Full guideline: 6.2 & 6.5 It is not clear why asenapine and aripiprazole have not been included as options for acute mania. In section 6.5 for the full guideline there is a statement that the "GDG decided not to recommend interventions that have not been shown to be clinically efficacious for the treatment of acute mania (that is, asenapine…..)". However no data is presented in section 6.2 to justify this. Arirpirazole is not included in the list of non-efficacious treatments and again there is no justification in 6.2 or 6.5 as to why it is not included. Rather there is only a statement in section 6.2.5 that it has a high acquisition cost.	Thank you for your comment. We have now amended the statement in section 6.5, as asenapine and ziprasione have indeed been shown to be efficacious compared with placebo for the treatment of mania. In section 6.2 we have added a description of the ranking of drugs by their overall probability to be best treatment according to their combined efficacy and acceptability, as reported in Cipriani et al. network meta-analysis. According to this analysis, aripiprazole ranked 6th and asenapine ranked 10th among 14 treatment options (including placebo). Moreover, aripiprazole and asenapine have

					There is a strong argument to include these two drugs. As is stated in 6.5 “service users may have different preferences based on prior experience and they may value side effects differently”. Two major references to asenapine in mania are omitted, even to be discounted e.g. asenapine (mean 18.2 mg/d) was rapidly effective, well tolerated and as effective as olanzapine (n = 488, RCT, d/b, p/c, 3/52, McIntyre et al, Bipolar Disord 2009; 11: 673–86), superior to placebo at day 2 and with less weight gain than olanzapine (n = 488, RCT, d/b, p/c, 3/52, McIntyre et al, J Affect Disord 2010; 122: 27–38). Aripirpazole is licensed to treat acute mania and also licensed for subsequent maintenance treatment. When the tolerability of antipsychotic drugs is considered then both drugs have a relatively favourable tolerability profile (Haddad PM, Sharma S. CNS Drugs 2007; 21(11):911-36). Finally aripiprazole will shortly be available as a generic which should reduce its acquisition cost. There has been an over-reliance on the Cipriani et al. 2011 multiple treatment metanalysis in coming to conclusions about treatment of acute mania, without acknowledging the shortfalls of this analysis. For example, this analysis includes the Khann et al. 2005 B J Psych study of risperidone conducted in India. This showed a drug-placebo difference in the order of 12-13 YMRS points after 3 weeks. This is way more than all the other large RCTs of antipsychotics in acute mania. For comparison another risperidone RCT showed just over a 5 point difference (Hirschfiled et al. Am J Psych 2004) – very in keeping with other antipsychotics. The difference in the Indian study was that baseline YMRS scores were over 37. Baselines in most large industry conducted mania studies are in the order of 29-30 demonstrating that the Indian patients were markedly more severely ill. The completion rate in the Indian study was over 95% which again is much higher than most large industry studies in acute mania (usually around the 65-70% mark). This will help	higher acquisition costs compared with the other drugs for acute mania that were assessed in the economic analysis. Both drugs were shown not to be cost-effective in the guideline economic analysis as they were dominated by other treatment options. We do acknowledge the fact that aripiprazole will soon be available as generic, and we have highlighted the need for re-assessment of cost effectiveness of drugs when these become generic [section 6.2.5, in *discussion – limitations of the economic analysis*]. The need for re-assessment of the cost effectiveness of aripiprazole for the treatment of mania once it has become generic has been noted by the Surveillance team at NICE. Regarding the two McIntyre papers, these had been included in the Cipriani et al network meta-analysis published in the Lancet in 2011 (McIntyre 2009 is reference 23 on page 15 and the second one is reference 6 on page 18 of the Supplementary webappendix of the Lancet paper). The second one is reported with the "unpublished name" of A7501004 because it was included in the analyses before its journal publication. On page 19 and 20 for the same supplementary file you can check the study characteristics. Regarding the issue about inclusion of Khanna 2005, this study has been included in the network meta-analysis because it met the pre-defined inclusion criteria, according to the review protocol (see corresponding Appendix in Cipriani et al., 2011 – Lancet). It should be noted that although the mean drug-placebo difference is greater in Khanna than the other studies, so is the variance. Therefore, the SMD is within the confidence intervals of most other

					accentuate the drug-placebo difference. Clearly the population was rather different in the Indian study and this in part explains the large effect size seen. However adding this one study with such a large effect size into the multiple treatment meta-analysis has distorted the data with regards to risperidone in comparison with other drugs not tested in a simpler population. We recommend that these caveats are at least acknowledged.	study SMDs. Nevertheless, in order to address your comment about over-reliance on data from this network meta-analysis, we carried out two sensitivity analyses excluding Khanna 2005 (both for efficacy and acceptability) and we found that results were materially no different: Efficacy (continuous data) Original analysis including Khanna2005: SMD -0.59 (95% CI -0.76, -0.42); I^2 = 44% Sensitivity analysis excluding Khanna2005: SMD -0.51 (95% CI -0.66, -0.37); I^2 = 0% Acceptability (drop-out rate, dichotomous outcome): Original analysis including Khanna2005: RR 0.50 (95% CI 0.38, 0.66); I^2 = 1% Sensitivity analysis excluding Khanna2005: RR 0.57 (95% CI 0.42, 0.78); I^2 = 0% This information will be added to the full guideline report.
British Association for Psychopharmacology	12	NICE	1.5.5	25	We are not clear about the recommendation that Li, in preference to valproate, is added to an antipsychotic in an episode of mania that has only partially responded to an antipsychotic. Many factors need to be considered in this clinical scenario and it is often far more acceptable to a patient and the clinical team to add valproate to an antipsychotic especially in a male patient. Lithium has the drawback that the dose can only be increased about every 10 days (7 days to get steady state and then inevitably several days waiting for the lithium level to come back from the lab). Valproate often allows you to achieve control of mania in a shorter time period than lithium. The footnote that sodium valproate does not have marketing authorisation for some indications may confuse: perhaps the semisodium valproate part could	Thank you for your comment. We agree that the evidence supporting the use of lithium and valproate as additional treatments to antipsychotics for acute mania is comparable. However, the GDG considered lithium as the preferred choice of drug as it has a better profile than valproate in the long term management of bipolar disorder. As with all NICE guidelines, this has to be used with clinical judgement and if there were clinical circumstances in which valproate might be preferable to lithium then the prescriber would select valproate over lithium in that situation.

					be placed earlier so as not to possibly confuse people that valproate itself isn't licensed	
British Association for Psychopharmacology	13	NICE	1.6.3	27	It is surprising that some much weight has been given to the use of olanzapine plus fluoxetine in the management of bipolar depression when this is based on relatively weak studies with low numbers of patients treated with the combination and no fluoxetine only arm (e.g. Tohen et al. Arch Gen Psych 2003 – combination n= 82, placebo n = 355 and olanzapine only n = 351). It is even more surprising that any recommendation is made about olanzapine monotherapy for bipolar depression. Reviewing the evidence suggest that even if there is a significant difference in MADRS score between olanzapine and placebo, this is driven entirely by non-specific effects of olanzapine. For example in the Tohen et al. 2003 study, compared to placebo, olanzapine monotherapy significantly reduced "inner tension" and increased sleep and appetite. However there was no significant effect on apparent or reported sadness or pessimistic thoughts (all of which improved on olanzapine plus fluoxetine). The data is most clear for quetiapine in the management of bipolar depression and we feel this should be acknowledged with this drug being the first to be mentioned. There may be a difference in Asian populations with olanzapine monotherapy possibly being more clearly effective (Tohen M B J Psych 2012), which is not mentioned anywhere – which is strange given that it is explicitly stated that differences between ethnic groups would be considered.	Thank you for raising these issues. With regard to the combination of fluoxetine and olanzapine, we used a network meta-analysis, which allows both direct and indirect evidence to be included in one model. However, the GDG did take into account your concern about the low numbers of participants in the combination studies, but on balance believe that the recommendation should stand. With regard to quetiapine, as described in section 6.5.2 of the full guideline "GDG determined that service users may have different preferences based on prior experience, and they may value side effects differently. For these reasons, the GDG decided to recommend that service users and clinicians choose among several pharmacological interventions with favourable ratios of benefits to harms." With regard to a differential treatment effect in Asian populations, although this is an important issue, there is insufficient evidence to draw conclusions at this stage (we note that Tohen do not make this claim).
British Association for Psychopharmacology	14	NICE	1.6.3 (to 1.6.7)	27 28	Many audits have demonstrated that many patients with bipolar disorder in the UK are prescribed antidepressants. Some guidance needs to be provided regarding this. At the very least there should be a statement that antidepressants should not be used alone in the absence of an antimanic treatment especially in patients with bipolar I "If a person develops moderate or severe bipolar depression and is already taking valproate, consider	Thank you for your comments. The GDG has carried out a systematic search of studies of the effects of antidepressants on mania and switching into mania and hypomania, and found inconsistent evidence of a possible very small adverse effect of antidepressants on switching. As a result the GDG decided to make only a 'consider stopping the antidepressant' recommendation if a person

					increasing the dose “ We were unaware of any evidence for positive dose response for valproate in bipolar depression.	was taking antidepressants and developed mania or hypomania. The GDG was not able to make any recommendation on the long-term use of antidepressants in view of this inconsistent evidence. Revised recommendation number 1.6.5 has been amended to reflect that the dose of valproate should only be increased so that the blood level is within the therapeutic range. The GDG agrees there is no evidence for the effectiveness of valproate doses above the therapeutic range.
British Association for Psychopharmacology	15	NICE	1.7.3	30	“Offer a structured, manualised psychological intervention (individual, group or family) designed for bipolar disorder to prevent relapse or for people who have some persisting symptoms between episodes of mania or bipolar depression.” Such an intervention may be designed for bipolar disorder but no quality evidence is put forward for efficacy.	Thank you for your comment. As described in section 8.2 of the full guideline, the GDG concluded that the evidence suggests that psychological interventions may improve symptoms and reduce the risk of relapse and hospitalisation for people with bipolar depression. This evidence is presented in section 8.1 of the full guideline. However, the GDG acknowledged that the evidence for particular psychological interventions varies in quality. The GDG also noted that the evidence for psychological interventions for unipolar depression is consistent with the evidence for bipolar depression and of much higher quality.
British Association for Psychopharmacology	16	NICE	1.7.5	31	The directive to explain to patients “that lithium is the most effective long-term treatment for bipolar disorder” is hard to substantiate with evidence. Apart from the Balance study where it was superior to valproate, we are not aware of any other long term study in bipolar disorder where lithium was shown to be superior to other long term treatment options	Thank you for your comment. As acknowledged in the full guideline (7.5) the evidence base is relatively poor and the GDG used their expert judgement when drafting this recommendation. Having considered this further, they stand by the recommendation.
British Association for Psychopharmacology	17	NICE	1.7.5	31	I am surprised that valproate has such a prominent place in long term treatment options. There is only one placebo controlled maintenance study of valproate (Bowden et al. 2000) which was entirely negative. The Balance study showed it to be less effective than lithium, however there was no placebo so we do not	Thank you for your comment. We were unable to carry out a meta-analysis as the trials were not conducted in a similar enough way. Therefore a narrative synthesis of RCTs was done. The GDG placed greater weight on the considerations of the Balance trial due to the

					know what valproate alone's efficacy is from this study. It is also surprising that ariprprazole and asenapine have not been included as long term options for patients who have responded to them acutely (as per the recommendation for quetiapine).	care with which it was undertaken, and the power and clinical significance of the trial. Other comparable trials tended to be discontinuation trials. In section 6.2 of the full guideline we have added a description of the ranking of drugs by their overall probability to be best treatment according to their combined efficacy and acceptability, as reported in Cipriani et al. network meta-analysis. According to this analysis, aripiprazole ranked 6th and asenapine ranked 10th among 14 treatment options (including placebo). Moreover, aripiprazole and asenapine have higher acquisition costs compared with the other drugs for acute mania that were assessed in the economic analysis. Both drugs were shown not to be cost-effective in the guideline economic analysis as they were dominated by other treatment options. We do acknowledge that aripiprazole will soon be available as generic, and we have highlighted the need for re-assessment of cost effectiveness of drugs when these become generic [section 6.2.5, in *discussion – limitations of the economic analysis*].The need for re-assessment of the cost effectiveness of aripiprazole for the treatment of mania once it has become generic has been noted by the Surveillance team at NICE.
British Association for Psychopharmacology	18	NICE	1.10.3-1.10.6	35 36	Hypotension and hypertension with most widely used antipsychotics are rare side effects as long as the medications are prescribed appropriately and in line with SPC (e.g. you don't start immediately with a high dose of quetiapine) and significant side-effects will be picked up by history or routine blood pressure monitoring. Obtaining accurate measurements in acutely unwell patients is likely to be challenging.	Thank you for your comments. The GDG found evidence that there was occasionally substantial and even life threatening harm due to cardiovascular events even in people with unsuspected cardiovascular disease. Therefore whenever possible the cardiovascular checks recommended in the guidelines should be performed as

					There does not seem to be a good rationale for adding this routinely before starting treatment- although it is indicated if there are specific indications (e.g. clozapine is used, the pt has a history of cardiac disease or has presented with postural hypotension previously etc – clearly in these case P & BP monitoring is important).	recommended in the guideline.
British Association for Psychopharmacology	19	NICE	1.10.16	38	"Measure the person's serum lithium level every 6 months " This is inconsistent with the FULL guidelines, which state (p238, line 15) "According to the GDG expert opinion, laboratory tests that are required specifically for people receiving long-term therapy with lithium include: - At initiation of treatment: 3 tests of serum lithium concentration in order to establish the drug's therapeutic dose - Over 1 year: **four** tests of serum lithium concentration, two tests of renal function (urea, creatinine and electrolytes); two tests of thyroid function; and two tests of calcium levels. " We would strongly recommend remaining consistent with the full guideline not least because if you say 6-monthly, practically that results in every 6-9 months or longer in the community. To say 3 months at least results in 3 tests in a year in most people.	Thank you for your comment. The guideline development group has considered your and others' comments and have revised the recommendation to say that everyone taking lithium should have their levels checked every 3 months for the first year (see revised recommendation number 1.10.18)..
British Association for Psychopharmacology	20	NICE	1.10.26	39	It states that valproate should be stopped immediately if abnormal LFTs are detected. Mild elevation of LFTs is common with valproate, as it is with many anticonvulsant drugs, and is often transient or non progressive – it is not a reason to stop valproate. Please define what is meant by abnormal LFTs or write that clinical judgement is needed as to whether to stop valproate or continue it with closer monitoring of the LFTs.	Thank you. This is helpful. A footnote has been added to the recommendation that reads: *Although the absolute values of hepatic enzymes are a poor indicator of the extent of hepatic damage, it is generally accepted that if these are persistently elevated to over 3 times the upper normal limit, continuing to rise or accompanied by clinical symptoms, the suspected drug should be withdrawn. Raised hepatic enzymes of any magnitude accompanied by reduced albumin or impaired clotting suggest severe liver disease.*
British Association	21	NICE	1.11.10	42	It is not clear why it is recommended to not continue	Thank you for your comment. The

for Psychopharmacology					antipsychotic treatment beyond 12 weeks when treating a young person for mania. It may take longer than 12 weeks to achieve stability, particularly if the first antipsychotic used is ineffective. In many cases when an antipsychotic has been effective one would want to continue it as a maintenance treatment especially if there is good evidence for such use (quetiapine, olanzapine and aripiprazole are all licensed as maintenance agents in BPD and although not licensed there is good evidence that risperidone is effective in preventing manic relapse in patients who had a manic episode that responded to risperidone)	recommendation on aripiprazole comes from the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be "routinely" continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
British Association for Psychopharmacology	22	NICE	1.10.26	39	It states that valproate should be stopped immediately if abnormal LFTs are detected. Mild elevation of LFTs is common with valproate, as it is with many anticonvulsant drugs, and is often transient or non progressive – it is not a reason to stop valproate. We suggest stating that clinical judgement is needed as to whether to stop valproate or continue it with closer monitoring of the LFTs.	Thank you. This is helpful. A footnote has been added to the recommendation that reads: *Although the absolute values of hepatic enzymes are a poor indicator of the extent of hepatic damage, it is generally accepted that if these are persistently elevated to over 3 times the upper normal limit, continuing to rise or accompanied by clinical symptoms, the suspected drug should be withdrawn. Raised hepatic enzymes of any magnitude accompanied by reduced albumin or impaired clotting suggest severe liver disease.*
British Association for Psychopharmacology	23	NICE	1.11.10	42	It is not clear why it is recommended to not continue antipsychotic treatment beyond 12 weeks when treating a young person for mania? It may take longer than 12 weeks to achieve stability, particularly if the first antipsychotic used is ineffective. In many cases when an antipsychotic has been effective one would want to continue it as a maintenance treatment especially if there is good evidence for such use (quetiapine, olanzapine and aripiprazole are all licensed as maintenance agents in BPD and although not licensed there is good evidence that risperidone is effective in preventing manic relapse in patients who	Thank you for your comment. The recommendation on aripiprazole comes from the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be

					had a manic episode that responded to risperidone)	"routinely" continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
Cheshire & Wirral Partnership NHS Trust	1	NICE	1.3.1	22	"Assessment of people with suspected bipolar disorder should be conducted in early intervention in psychosis services". This would be realistically difficult to implement because of the following; 1. No robust evidence as yet to support the effectiveness of EI services in Bipolar over treatment as usual 2. No robust evidence to demonstrate that the expertise in EI in psychosis can directly translate into the management of Bipolar Disorder 3. The two conditions are fundamentally different for instance with a peak of onset in the mid-forties for Bipolar, which is beyond the cut-off point for most EI psychosis services 4. Obvious commissioning issues. 5. Lack of consistency in the diagnosis of Bipolar in early stages underpinned by lack of biological markers and considerable overlap of symptoms with other syndromes.	Thank you for your comment. The psychosis and schizophrenia guideline looked at the evidence underpinning the use of EIS services for people with suspected and early psychosis. These populations include people who later develop schizophrenia, bipolar disorder and other psychoses. All the trials included were with mixed populations. We accept that schizophrenia and bipolar are different conditions, with different guidelines. However, there is considerable overlap in the treatment and management of these conditions. It is also important that, for both groups access to a service that works on the principle of early intervention is important. The GDG does however concede that there is some variation in service provision, and has therefore revised the recommendation to set out the components of the teams that should provide assessment for bipolar disorder, rather than stating that the team must be EIS.
Cheshire & Wirral Partnership NHS Trust	2	Full	5.3.3	101 104	It would seem that the recommendation above is from the CDG judging that the early intervention in psychosis service would provide the best service configuration for people with bipolar disorder; please refer to above comments. This is a very weak evidence to bring a recommendation with potentially so much impact in service delivery.	Thank you for your comment. The GDG developed the components for assessment using consensus methods and based on reviews of other NICE guidelines. The recommendations relating to service configuration for assessment have now however been revised. The psychosis and schizophrenia guideline looked at the evidence underpinning the use of EIS services for people with suspected and early psychosis. These populations include people who later develop schizophrenia, bipolar disorder and other psychoses. All the trials included were with mixed populations. We accept that schizophrenia and bipolar are

						different conditions, with different guidelines. However, there is considerable overlap in the treatment and management of these conditions. It is also important that, for both groups access to a service that works on the principle of early intervention is important. The GDG does however concede that there is some variation in service provision, and has therefore revised the recommendation to set out the components of the teams that should provide assessment for bipolar disorder, rather than stating that the team must be EIS. Recommendation 1.3.5 has been merged with revised recommendation 1.3.1.
Cheshire & Wirral Partnership NHS Trust	3	NICE/Full	1.3.5/ 5.6.1.8	108	Same comments as above: It would seem that the recommendation above is from the CDG judging that the early intervention in psychosis service would provide the best service configuration for people with bipolar disorder; please refer to above comments. This is a very weak evidence to bring a recommendation with potentially so much impact in service delivery.	Thank you for your comment. The GDG developed the components for assessment using consensus methods and based on reviews of other NICE guidelines. The recommendations relating to service configuration for assessment have now however been revised. The psychosis and schizophrenia guideline looked at the evidence underpinning the use of EIS services for people with suspected and early psychosis. These populations include people who later develop schizophrenia, bipolar disorder and other psychoses. All the trials included were with mixed populations. We accept that schizophrenia and bipolar are different conditions, with different guidelines. However, there is considerable overlap in the treatment and management of these conditions. It is also important that, for both groups access to a service that works on the principle of early intervention is important. The GDG does however concede that there is some variation in service provision, and has therefore revised the recommendation to set out the components of the teams that should provide assessment for bipolar disorder, rather

						than stating that the team must be EIS. Recommendation 1.3.5 has been merged with revised recommendation 1.3.1.
Cheshire & Wirral Partnership NHS Trust	4	Full	5.1.3		To consider adding NICE guidance on the management of Depression, and Electroconvulsive Therapy. Both Depression and Mania are listed as conditions for which ECT is demonstrated to be efficient.	Thank you for your comment. The use of ECT is outside the scope of this guideline as it is dealt with in the guideline on (unipolar) depression. (NICE CG90). However, the guideline development group has added a recommendation cross-referring to the NICE technology appraisal on the use of ECT for severe mania that has not responded to other interventions (see revised recommendation 1.5.11).
Cheshire & Wirral Partnership NHS Trust	5	Full	5.2		The NICE guidance on Psychosis is now released rather than “expected”.	Thank you, all references to the Psychosis guideline have been amended.
Cheshire & Wirral Partnership NHS Trust	6	NICE	1.5.3	11	Aripiprazole and asenapine are also licensed for the treatment of mania. It is supported as such in the British National Formulary (BNF) and listed as first line options in the CANMAT (Bipolar Disorders 2013; 15: 1-44). The BNF also outlines the risk of toxicity when combining Lithium with Haloperidol and Flupentixol including of irreversible toxic encephalopathy.	Thank you for your suggestion. NICE guidelines recommend interventions that are most clinically and cost effective, based on best available evidence. Aripiprazole and asenapine are licensed for manic episodes but they appear to be less effective and cost-effective than other drugs: The Cipriani et al. network meta-analysis, which was the main source of clinical evidence on drugs for mania that was utilised in this guideline, showed that aripiprazole ranked 6th and asenapine ranked 10th among 14 treatment options (including placebo) in terms of combined efficacy and acceptability. Aripiprazole and asenapine had also the highest acquisition costs among the drugs considered and were therefore overall less clinically and cost-effective than the drugs that are recommended in this guideline. Numerous recommendations (1.5.6, 1.5.8) in the guideline refer the reader to consider the advice given by the BNF. The guideline does

						not recommend Flupentixol.
Cheshire & Wirral Partnership NHS Trust	7	NICE	1.5.2	24	If somebody develops mania or hypomania…start a mood stabiliser (rather than just antipsychotic; to include consideration for Lithium or Valproate)	Thank you for your comment. The network meta-analysis that the GDG decided to use showed that a number of specific antipsychotic drugs were more effective and better tolerated than lithium or valproate. The GDG has avoided the use of the term mood stabiliser as there is little consensus on the meaning of the term.
Cheshire & Wirral Partnership NHS Trust	8	NICE	1.7	30	Various psychological interventions can be efficacious in Bipolar Disorder; present a CHOICE rather than a list.	Thank you, we have listed the therapies which have evidence of benefit and characterised them based on the trials which show a positive effect in reducing relapse rates.
Cheshire & Wirral Partnership NHS Trust	9	NICE	1.9	33	Refer to comment 1: “Assessment of people with suspected bipolar disorder should be conducted in early intervention in psychosis services”. This would be realistically difficult to implement because of the following; 1. No robust evidence as yet to support the effectiveness of EI services in Bipolar over treatment as usual 2. No robust evidence to demonstrate that the expertise in EI in psychosis can directly translate into the management of Bipolar Disorder 3. The two conditions are fundamentally different for instance with a peak of onset in the mid-forties for Bipolar, which is beyond the cut-off point for most EI psychosis services 4. Obvious commissioning issues. 5. Lack of consistency in the diagnosis of Bipolar in early stages underpinned by lack of biological markers and considerable overlap of symptoms with other syndromes.	Thank you for your comment. The psychosis and schizophrenia guideline looked at the evidence underpinning the use of EIS services for people with suspected and early psychosis. These populations include people who later develop schizophrenia, bipolar disorder and other psychoses. All the trials included were with mixed populations. We accept that schizophrenia and bipolar are different conditions, with different guidelines. However, there is considerable overlap in the treatment and management of these conditions. It is also important that, for both groups access to a service that works on the principle of early intervention is important. The GDG does however concede that there is some variation in service provision, and has therefore revised the recommendation (1.9.1 and 1.3.1) to set out the components of the teams that should provide assessment for bipolar disorder, rather than stating that the team must be EIS.
Cheshire & Wirral Partnership NHS Trust	10	NICE	1.10.6	36	Plan for monitoring of Prolactin for people on First Generation Antipsychotics.	Thank you for raising the important point of physical health issues in people taking antipsychotics. We have amended the recommendation to include the monitoring of physical health.

Cheshire & Wirral Partnership NHS Trust	11	NICE	1.5.1	24	Consider suggesting recommendations by responsible clinicians to people experiencing an acute phase of the bipolar disorder on the fitness to drive accordingly to the DVLA guidance (accessible on line https://www.gov.uk/current-medical-guidelines-dvla-guidance-for-professionals)	Thank you for your comment, recommendation 1.3.5 states that the risks associated with driving should be included in a risk assessment.
Cheshire & Wirral Partnership NHS Trust	12	NICE	1.5.2	24	The NorthWest has developed a restricted formulary for which the most expensive molecules can be accessed only on a named-patient basis. The rational presented is "to advance cost-effective, evidence-based prescribing, in line with NICE Clinical Guidance 38". It actually creates a postcode prescribing lottery as some Trusts are more flexible than others on the access of those molecules. This therefore contributes to inacceptable regional variations of care. The molecules targeted are Aripiprazole, Quetiapine XL. Asenapine hasn't been included in the formulary of numerous Trusts.	Thank you. This does sound like an unintended consequence of blanket rules for prescribing.
Cheshire & Wirral Partnership NHS Trust	13	NICE	General	General	Might be helpful to expand on the prescribing and monitoring in the perinatal period for patients suffering from Bipolar, or refer to a NICE guidance on the topic if still up to date.	Thank you for your comment. The guideline development group agrees that this is an important issue, but it is one that is covered by another guideline, Antenatal and Postnatal Mental Health, which is currently being updated. The bipolar disorder guideline contains a cross-reference to this guideline in revised recommendation number 1.1.4.
College of Mental Health Pharmacy	1	Full	6.5.2	167 line 36 (to 41)	We are surprised that asenapine and aripiprazole are omitted. There is a statement in the full guidelines that ""*Asenapine and aripiprazole are associated with considerably higher drug acquisition costs and may be less efficacious than other medications for mania*." As we understood it lithium, quetiapine, valproate, ziprasidone, carbamazepine aripiprazole and asenapine are of similar efficacy, and aripiprazole was as effective as quetiapine (s=68, n=16073, RCT, 3/52, Cipriani *et al, Lancet* 2011; 378: 1306–15). Is the GDG now saying it does not believe Dr. Cipriani's own meta-analysis? If so, I think we should be told. Two major references to asenapine in mania are omitted e.g. asenapine (mean 18.2 mg/d) was rapidly	Thank you for your comment. The GDG does believe Dr Cipriani's meta-analysis. In section 6.2 we have added a description of the ranking of interventions by their overall probability to be best treatment according to their combined efficacy and acceptability, as reported in Cipriani et al. According to this analysis, aripiprazole ranked 6th and asenapine ranked 10th among 14 treatment options (including placebo). We have also amended the statement you refer to, which now reads: "Asenapine and aripiprazole are associated with considerably higher drug acquisition costs and may be

					effective, well tolerated and as effective as olanzapine (n=488, RCT, d/b, p/c, 3/52, McIntyre *et al, Bipolar Disord* 2009;11:673–86) and superior to placebo at day 2 and with less weight gain than olanzapine (n=488, RCT, d/b, p/c, 3/52, McIntyre *et al, J Affect Disord* 2010;122:27–38). Whilst asenapine and aripiprazole may have a higher acquisition cost at the moment, they are both effective treatments and should not be excluded as some patients may prefer these, especially if they have had adverse effects from past treatments.	overall less effective than other medications for mania considering their ranking in terms of combined efficacy and acceptability". Whilst asenapine and aripiprazole are at the moment more expensive than other drugs, we do acknowledge the fact that these will eventually become generic and thus we have now highlighted the need for re-assessment of the cost effectiveness of drugs once they become generic [section 6.2.5, in discussion – limitations of the economic analysis]. Regarding the included studies, the two McIntyre papers had been included in Cipriani et al NMA published in the Lancet in 2011 (McIntyre 2009 is reference 23 on page 15 and the second one is reference 6 on page 18 of the Supplementary webappendix of the published paper – see file: ///H:/Pubblicazioni/MTM%20acute%20mania/Supplementary%20material_Lancet.pdf). The second one is reported with the "unpublished name" of A7501004 because it was included in the analyses before its journal publication. On page 19 and 20 of the same supplementary file you can check the study characteristics.
College of Mental Health Pharmacy	2	NICE	General	5 (onwards)	Throughout this document, starting on p5, you use the term "Person-centered care" and later "person" and "young person". This is consistent and helpful terminology. However, you also start using the term "service user" as well (which is inconsistent) and not "patient", which is the RCPsych preferred term. Please either move to using "person" throughout or, failing that, "patient", or at least use "patient" when referring to people who are admitted into a hospital.	Thank you for your comment. The guideline only uses the term 'service user' when referring to other NICE guidance entitled 'Service User Experience in Adult Mental Health'; in the rest of the guideline the term 'person with bipolar disorder' or 'person' is used.
College of Mental Health Pharmacy	3	Full	6.5.3	169 line 37-38	"*Asenapine and aripiprazole are associated with considerably higher drug acquisition costs and may be less efficacious than other medications for mania*." As we understood it: ▪ Lithium, quetiapine, valproate, ziprasidone,	Thank you for your comment. In section 6.2 we have now added a description of the ranking of drugs by their overall probability to be best treatment according to their combined efficacy and acceptability, as reported in Cipriani et al.

					carbamazepine aripiprazole and asenapine are of similar efficacy (s=68, n=16073, RCT, 3/52, Cipriani *et al, Lancet* 2011; 378: 1306–15; s=56, n=10,800, RCT, p/c, Yildiz *et al, Neuropsychopharmacology* 2011;36:375–89).	network meta-analysis. According to this analysis, aripiprazole ranked 6th and asenapine ranked 10th among 14 treatment options (including placebo). We have also amended the statement you quote, which now reads: "Asenapine and aripiprazole are associated with considerably higher drug acquisition costs and may be overall less effective than other medications for mania considering their ranking in terms of combined efficacy and acceptability".
College of Mental Health Pharmacy	4	General (both)	General	General	We are surprised that the study by "Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, et al. Cognitive behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. British Jounal of Psychiatry. 2006;188:313-20" (NB note misspelling of Journal) has become part of the evidence *for* psychological therapies but was essentially a failed or negative study showing no effect overall except perhaps in some people with fewer episodes. This contrasts with the attitude taken towards asenapine and aripiprazole, where different criteria for efficacy are used.	Thank you for your comment, but we believe the GDG followed good practice by including all studies that met the pre-specified eligibility criteria regardless of outcome. Where possible, meta-analysis was used to estimate the magnitude of effect, and the GRADE approach was used to determine our confidence in these estimates. Thank you for pointing out the spelling mistake, this has been corrected.
College of Mental Health Pharmacy	5	NICE	General	General	All the recommendations about psychological therapies make an assumption that the patient speaks English fluently and is capable of engaging in therapy. This ignores the very many people who have arrived in UK or were born here who do not speak English fluently but still have significant mental health problems. If there is evidence that these therapies are effective for other ethnic groups and cultures this needs to be stated. If not, this limitation also needs to be made clear as well. The Scott et al (2006) study used real-world samples rather than selected patients, but of course that showed no overall effect. We're sure your predominantly English-speaking Caucasian GDG wouldn't want to be branded with any	Thank you for your comments. The guideline recommends that professionals working with children and young people with bipolar disorder should heed the recommendations in the general principles of care in the psychosis and schizophrenia guideline, which includes a substantial section on ethnicity, minorities and therapy with non-English speaking people. A recommendation has been added to also reference the relevant section on race, culture and ethnicity from the psychosis and schizophrenia in adults' guideline, which also addresses these issues.

					diversity or discrimination accusations.	
College of Mental Health Pharmacy	6	NICE	1.2.5	10	Ref: Offering high-intensity psychological interventions based on an extrapolation from unipolar depression. We hadn't realised that bipolar depression was the same as unipolar depression, which would no doubt come as a shock to people suffering from either condition. To suggest two different conditions with overlapping symptoms are essentially the same without any positive evidence (and in the face of evidence to the contrary) seems naive in the extreme. If only antidepressants worked for both. But they don't.	Thank you. High intensity psychological treatments in primary care are those already provided by IAPT services. CBT and IPT can be delivered in primary care for people with moderate to severe depressive episodes, irrespective of the cause/type of depression. Indeed, one in 10 people with depression turn out to have bipolar disorder, so IAPT will already be doing this work with depressed people where it is not known whether it is a unipolar or a bipolar depression. The GDG concluded that it made no difference in terms of technique or skill whether CBT was being provided for people with uni- or bi-polar depression. The method of treatment is essentially the same. Therefore, IAPT services should offer psychological therapies for people with bipolar disorder who are currently depressed.
College of Mental Health Pharmacy	7	NICE	0	10	Not recommending quetiapine Quetiapine is widely used by GPs, has a clearly defined dose range, needs little monitoring, is easily and quickly available, and the response is 60% vs 30% with placebo. These effects were shown within 6 weeks, proven in bipolar depression, and shown in full, independent RCTs with proper placebo groups and controls (no waiting list control groups).	Thank you for your comment. The guideline does recommend quetiapine for both mania and bipolar depression, but given that most people will be first treated in an early intervention service or by a specialist bipolar disorder or integrated community-based team, use of quetiapine has not been specifically outlined for primary care.
College of Mental Health Pharmacy	8	NICE	0	10	GPs should also be encouraged to stop prescriptions for antidepressants and advise patients to stop taking them if they become hypomanic.	Thank you for your comment. The GDG took the view that such decisions should be made in secondary care because most general practitioners would not have the expertise or confidence to do this.
College of Mental Health Pharmacy	9	NICE	1.5.3	11	You need to be very clear here why you are specifically excluding aripiprazole and asenapine from this list of drugs.	Thank you for your suggestion. NICE guidelines recommend interventions that are most clinically and cost effective, based on best available evidence. Section 6.2 has been amended to include a description of the ranking of drugs by their overall probability to be best treatment

						according to their combined efficacy and acceptability, as reported in Cipriani et al. network meta-analysis. According to this analysis, aripiprazole ranked 6th and asenapine ranked 10th among 14 treatment options (including placebo). Moreover, aripiprazole and asenapine have higher acquisition costs compared with the other drugs for acute mania that were assessed in the economic analysis. Both drugs were shown not to be cost-effective in the guideline economic analysis as they were dominated by other treatment options.
College of Mental Health Pharmacy	10	NICE	1.5.3	11	It would appear to read as an oversight that there is not reference to the use of valproate as an antimanic.	Thank you for your comment. In the network meta-analysis by Cipriani et al, updated and used in this guideline, valproate and the other mood stabilisers were significantly less effective than the antipsychotics.
College of Mental Health Pharmacy	11	NICE	1.5.3	11	It would be better to be person-specific i.e. to reiterate that if a patient has stopped treatment that had been effective (which is very commonly the case) then that effective treatment (antipsychotic or mood stabiliser) should be offered again.	Thank you for your comment. The GDG believes that the scenario you present is covered in recommendation 1.5.3 in relation to consideration of previous response to treatment.
College of Mental Health Pharmacy	12	NICE	1.6.3	11	Fluoxetine combined with olanzapine[2] The footnote implies that this combination is in common UK clinical practice. 1. We have carried out a survey of UK Trusts via the College of Mental health Pharmacy e-mail group. We have had 22 replies so far, with a 100% response that this is **not** a common practice. 2. We are surprised that the flawed studies on fluoxetine and olanzapine (OFC) were considered. We accept that it is licensed in the USA but, under your own criteria, licensing does not mean an inclusion. The study with OFC had no comparison with fluoxetine alone and so an effect just from the fluoxetine in the combination cannot be excluded. The mild efficacy seemed to be non-specific effects from olanzapine, in the same way that historic studies showed benzodiazepines were	Thank you for your comments. We have changed the footnote. With regard to the combination of fluoxetine and olanzapine, we addressed this issue by using a network meta-analysis. This approach is more sophisticated than using traditional pairwise meta-analyses, and allows both direct and indirect evidence to be included in one model. With regard to quetiapine, as described in section 6.5.2 of the full guideline “GDG determined that service users may have different preferences based on prior experience, and they may value side effects differently. For these reasons, the GDG

					effective for depression through an effect on the anxiety components of depression. 3. Quetiapine, as the clearly most effective agent, should be placed first.	decided to recommend that service users and clinicians choose among several pharmacological interventions with favourable ratios of benefits to harms."
College of Mental Health Pharmacy	13	NICE	1.6.3	12	Lamotrigine should not be used for acute bipolar depression, and should not be recommended as such because of the risk of prescribers trying to bypass the slow titration. We have heard clinical staff saying that the slow titration doesn't apply to bipolar. In addition, the effect of lamotrigine alone is modest, there are numerous failed trials. It may be useful as an adjunct to lithium though (Van der Loos J Clin Psych 2009). Therefore lamotrigine monotherapy cannot be recommended in the acute phase, it can only be recommended for prophylaxis.	Thank you. The network meta-analysis underpinning this recommendation does suggest that lamotrigine is effective in the treatment of bipolar depression, hence the guideline recommends its use. Further recommendations on the use of lamotrigine have been added to section 1.10 to aid clinicians.
College of Mental Health Pharmacy	14	NICE	1.6.1	12	For consistency you should add to psychological interventions: "*Discuss with the person the possible benefits and risks for this intervention*" e.g. discomfort, withdrawal symptoms, duration, lack of efficacy in mania, homework, possibility of not liking the therapist, not speaking the same language etc. Unless of course there are no possible adverse consequences of psychological interventions, in which case evidence to prove this should be included.	Thank you for your comment, with which the Guideline Development Group agrees. The sentence you have suggested has been added to the recommendation.
College of Mental Health Pharmacy	15	NICE	1.11.4	13	Please clarify age in brackets (e.g. 13-18 years?)	Thank you for your comment – 'young people' is defined at the start of the recommendations, therefore we do not feel it is necessary to repeat this here.
College of Mental Health Pharmacy	16	NICE	1.11.12	14	What if the person declines a structured, manualised psychological intervention as having no evidence of efficacy in bipolar depression?	Thank you. It is perfectly acceptable for service users to refuse any treatment unless they are subject to the mental health act and then in only very specific circumstances, which do not include psychological treatments. However, as psychological therapies do have evidence of benefit, it would be right to tell the service user of these benefits (reduced relapse rates) before they refuse such treatments.

College of Mental Health Pharmacy	17	NICE	1.11.11	14	"*do not offer valproate to girls of child bearing age*". The previous guidelines used the term child-bearing potential, arrived at after much discussion. We think this statement needs to be either toned down or explained. You haven't stated why, because if a girl/young woman is not sexually active or cannot have children then the concern about teratogenicity is irrelevant. Furthermore, sometimes the risk of teratogenicity with valproate may be a reasonable option and even the patients' preference compared to the significant weight gain with olanzapine, and need for detailed adherence with lithium.	Thank you for your comment, however the guideline only uses the phrase 'childbearing potential'.
College of Mental Health Pharmacy	18	NICE	1.2.4	19 20	GPs should be encouraged to stop any current prescriptions for antidepressants, and advise patients to stop taking them if they become hypomanic.	Thank you for your comment. The GDG took the view that such decisions should be made in secondary care because most general practitioners would not have the expertise or confidence to do this.
College of Mental Health Pharmacy	19	NICE	1.2.7	20	Rephrase such that it is very clear that this mean do not start FOR THE FIRST TIME, but GPs can and should re-instate lithium that the patient has discontinued, in consultation with secondary care.	Thank you for your comment, this has now been clarified in the recommendation.
College of Mental Health Pharmacy	20	NICE	1.2.8	20	Re phrase such that it is very clear that this mean do not start FOR THE FIRST TIME, but GPs can and should re-instate valproate that the patient has discontinued, in consultation with secondary care.	Thank you, the GDG considered your comment but came to the decision that valproate should only be started in secondary care at any point.
College of Mental Health Pharmacy	21	NICE	1.2.9	20	Add "problematic" before "co-morbid alcohol or drug misuse", otherwise this sentence implies that every patient who occasionally has a joint of cannabis should be referred to secondary care.	Thank you. However, the terms used do not suggest occasional use: "comorbid substance misuse" is a widely used term which distinguishes substance use from misuse.
College of Mental Health Pharmacy	22	NICE	1.2.5	20	Not recommending quetiapine Quetiapine is widely used by GPs, has a clearly defined dose range, needs little monitoring, is easily and quickly available, and the response is 60% vs 30% with placebo. These effects were shown within 6 weeks, proven in bipolar depression, and shown in full, independent RCTs with proper placebo groups and controls. No waiting list control groups there.	Thank you for your comment. The guideline does recommend quetiapine for both mania and bipolar depression, but given that most people will be first treated in an early intervention service or by a specialist bipolar disorder or integrated community-based team, use of quetiapine has not been specifically outlined for primary care.
College of Mental Health Pharmacy	23	NICE	1.2.12	21	Please add thyroid function for lithium. That's a serious omission. Unless you have evidence to the contrary?	Thank you for your comment, monitoring thyroid function has been added to the recommendation.

College of Mental Health Pharmacy	24	NICE	1.2.12	21	Please add the word “annual” in again to emphasise the point “Ensure that the *annual* physical health checks include……”	Thank you for your suggestion, this has been added to the recommendation.
College of Mental Health Pharmacy	25	NICE	1.3.1	22	“*Assessment of people with suspected bipolar disorder should be conducted in early intervention in psychosis services*. “ Suggest re-wording this slightly difficult sentence e.g. “Assessment of people with suspected bipolar disorder should be conducted in Early Intervention ~~in Psychosis~~ services.“	Thank you for your comment. This recommendation has been revised. However, the term ‘early intervention in psychosis service’ has been retained for consistency with other guidelines.
College of Mental Health Pharmacy	26	NICE	1.4 1.5	24	1.4 would sit better after section 1.5.	Thank you for your comment, but the guideline development group preferred to keep the recommendations on acute episodes (sections 1.5 and 1.6) together.
College of Mental Health Pharmacy	27	NICE	1.5	24	This section does not convey any sense of urgency. Please add some text to emphasise this. Delaying proactive and effective therapy for a patient becoming (hypo)manic risks prolonging the duration of the full-blown manic episode and makes it much harder to treat, which is to the detriment of the patient and may well result in avoidable admission.	Thank you for your comment, recommendations 1.4.2, 1.4.3 address how to manage those in crisis.
College of Mental Health Pharmacy	28	NICE	1.5.1	24	“access to calming environments” – it is not clear to what you are alluding. Is this in the context of the patient’s own home? Or is this to be understood by organisations as a structural environment in a ward setting that they should provide?	Thank you for your comment. Indeed such calming environments may take different forms and could be in different settings, and even at different times e.g. sometimes homes and wards can be loud and not calming. Therefore the GDG consider that further detail should not be specified in the recommendation.
College of Mental Health Pharmacy	29	NICE	1.5.3	25	Asenapine, aripiprazole and valproate are missing here and this again needs some explanation	Thank you for your comment. NICE guidelines recommend interventions that are most clinically and cost effective, based on best available evidence. Aripiprazole, asenapine and valproate appear to be less effective and cost-effective than other drugs: The Cipriani et al. network meta-analysis, which was the main source of clinical evidence on drugs for mania that was utilised in this guideline, showed that aripiprazole ranked 6th, valproate ranked 7th and asenapine

						ranked 10th among 14 treatment options (including placebo) in terms of combined efficacy and acceptability. These 3 drugs have higher acquisition costs compared with the other drugs for acute mania that were assessed in the economic analysis. Both drugs were shown not to be cost-effective in the guideline economic analysis as they were dominated by other treatment options. We do acknowledge that aripiprazole will soon be available as generic, and we have highlighted the need for re-assessment of cost effectiveness of drugs when these become generic [section 6.2.5, in *discussion – limitations of the economic analysis*].The need for re-assessment of the cost effectiveness of aripiprazole for the treatment of mania once it has become generic has been noted by the Surveillance team at NICE.
College of Mental Health Pharmacy	30	NICE	1.5.5	25	We are really surprised at the suggestion to use lithium for acute mania ahead of valproate. Valproate is safer and easier to use, does not have the potential for discontinuation effects, is quicker-acting, and loading doses can be given safely without the need for invasive monitoring. There is also a risk of a negative impact for lithium, in that it really should have patient consent before starting as taking for insufficient duration may lead to a negative outcome.	Thank you for your comment. We agree that the evidence supporting the use of lithium and valproate as additional treatments to antipsychotics for acute mania is comparable. However, the GDG considered lithium as the preferred choice of drug as it has a better profile than valproate in the long term management of bipolar disorder.
College of Mental Health Pharmacy	31	NICE	1.5.5	25	Please acknowledge not just that “when lithium is ineffective” but that it (often) is “an inappropriate choice” e.g. if a patient flatly refuses any physical health investigations such as blood tests.	Thank you for your comment. The GDG agrees that there are occasions when the use of lithium is not suitable and therefore recommendation 1.5.5 has been amended.
College of Mental Health Pharmacy	32	NICE	1.5.5	25	You only seem to be recommending adding an antipsychotic to either lithium or valproate. Please acknowledge that at times other combinations are needed e.g. lithium with valproate, and/or all three.	Thank you for your comment. It is not possible for the guideline to detail every scenario and clinicians will need to use their judgement in these situations. We know of no evidence at this time to support lithium and valproate, or a combination of the two, with an antipsychotic.
College of Mental Health Pharmacy	33	NICE	General	General	The footnote that sodium valproate does not have marketing authorisation for some indications is	Thank you for your comment; the guideline development group has reordered the footnote

					reasonable but potentially misleading. Perhaps the semisodium valproate part could be placed earlier so as not to possibly confuse people that valproate itself isn't licensed.	as you have suggested.
College of Mental Health Pharmacy	34	NICE	1.6.3	27	*1.6.3 If a person develops moderate or severe bipolar depression and is not taking a drug to treat their bipolar disorder, offer fluoxetine combined with olanzapine, or quetiapine on its own, depending on the person's preference and previous response to treatment.* *If the person prefers, consider either olanzapine (without fluoxetine) or lamotrigine on its own.* *15 Although this use is common in UK clinical practice, at the time of publication (September 2014), lamotrigine did not have a UK marketing authorisation for this indication.* Lamotrigine is licensed for "Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes. Lamotrigine is not indicated for the acute treatment of manic or depressive episodes." Perhaps this footnote should make it clear that it is only unlicensed for acute bipolar depression. Lamotrigine should not be used for acute bipolar depression, and should not be recommended as such because: - It doesn't work - The risk of clinicians trying to bypass the slow titration. We have heard clinical staff saying that the slow titration doesn't apply to bipolar.	Thank you. The network meta-analysis underpinning this recommendation does suggest that lamotrigine is effective in the treatment of bipolar depression, hence the guideline recommends its use. Further recommendations on the use of lamotrigine have been added to section 1.10 to aid clinicians. Regarding the footnotes, lamotrigine is only recommended for acute bipolar depression, therefore the guideline development group does not consider that changing the footnote would be appropriate.
College of Mental Health Pharmacy	35	NICE	1.6.5	28	"*If a person develops moderate or severe bipolar depression and is already taking valproate, consider increasing the dose* " We were unaware of any evidence for positive dose response for valproate in bipolar depression.	Thank you for your comments. The GDG has carried out a systematic search of studies of the effects of antidepressants on mania and switching into mania and hypomania, and found inconsistent evidence of a possible very small adverse effect of antidepressants on switching. Revised recommendation number 1.6.5 has been amended to reflect that the dose of

						valproate should only be increased so that the blood level is within the therapeutic range. The GDG agrees there is no evidence for the effectiveness of valproate doses above the therapeutic range.
College of Mental Health Pharmacy	36	NICE	1.6	28	There's no reference at all to the potential role for ECT when all medicines fail to acute treat severe bipolar depression or mania for patients admitted to hospital. This needs to be clarified.	Thank you for your comment. The use of ECT is outside the scope of this guideline as it is dealt with in the guideline on (unipolar) depression. (NICE CG90). However, the guideline development group has added a recommendation cross-referring to the NICE technology appraisal on the use of ECT for severe mania that has not responded to other interventions (see revised recommendation number 1.5.11).
College of Mental Health Pharmacy	37	NICE	1.7.1	29	3rd bullet point says "risk of relapse after stopping medication" please amend to "reducing or stopping". And also rephrase the sentence to include the word adherence.	Thank you for your comment. The word 'reducing' has been added, which the guideline development group considers covers adherence by the patient and additional factors such as advice by a doctor.
College of Mental Health Pharmacy	38	NICE	1.7.3	30	"*Offer a structured, manualised psychological intervention (individual, group or family)* ***designed*** *for bipolar disorder to prevent relapse or for people who have some persisting symptoms between episodes of mania or bipolar depression*." Such an intervention may be **designed** for bipolar disorder but no quality evidence is put forward for its efficacy and so should not be included in an evidence-based guideline.	Thank you for your comment. As described in section 8.2 of the full guideline, the GDG concluded that the evidence suggests that psychological interventions may improve symptoms and reduce the risk of relapse and hospitalisation for people with bipolar depression. This evidence is presented in section 8.1 of the full guideline. However, the GDG acknowledged that the evidence for particular psychological interventions varies in quality. The GDG also noted that the evidence for psychological interventions for unipolar depression is consistent with the evidence for bipolar depression and of much higher quality.
College of Mental Health Pharmacy	39	NICE	1.7.7	32	"Before stopping medication, discuss with the person how to recognise early signs of relapse and what to do if symptoms recur. " We think you mean "If stopping…" not "Before stopping..."	Thank you for your comment, the recommendation has been changed to 'If stopping….'
College of Mental	40	NICE	1.8.4	32	"Routinely monitor weight…"	Thank you, but the guideline development

Health Pharmacy					Can we add a frequency? i.e. at least annually as per the Key Recommendations at the beginning.	group thinks it is clear it is annual because the recommendation mentions the 'annual team report'.
College of Mental Health Pharmacy	41	NICE	1.9	33	We should specifically add a subsection to 1.9 on "Adherence" as this is too crucial to omit and is a significant reason for relapse e.g. add within 1.9.2 where "intensive case management" is recommended, as assisting adherence is about assisting recovery, and self-management. Adherence should *not* sit in 1.10 which is essentially instructions to the prescriber about medicines.	Thank you. The GDG disagree that adherence should not sit in 1.10 – they decided it should be included in the recommendation on intensive case management, which is a specific service level intervention.
College of Mental Health Pharmacy	42	NICE	1.10.5	35	Each bullet point has a full stop, whereas only the last one should have one.	Thank you for your comment, but this is NICE style for some recommendations with long entry bullet points.
College of Mental Health Pharmacy	43	NICE	1.10.5	35	1.10.1 and 1.10.2 seem valid, but these seem unusual points to raise first in this way. We would have expected and hoped to see priority being given to principles such as patient choice, listening to the patients' preferences when recommending therapies, joint decision making, providing patients with written and verbal information, using the least number of medicines at the lowest effective doses etc. Only then moving on to these specific points. Some of these points are made later e.g. in 1.10.5 with specific reference to starting antipsychotics, but these principles should not be restricted just to antipsychotics and to this scenario.	Thank you for your comment, the guideline development group has drafted a new recommendation (revised recommendation 1.10.1) to cover the points you have raised.
College of Mental Health Pharmacy	44	NICE	1.10.9	36	Re "PRN" please would you explain that this refers to admitted "in-patients".	Thank you for your comment, but p.r.n in this content does not necessarily refer only to inpatient care. P.r.n medication is used very frequently in early interventions in bipolar disorder recommended through the guideline.
College of Mental Health Pharmacy	45	NICE	1.10.11	37	"*ensure the person is given the information they need to take lithium safely, for example the National Patient Safety Agency's information on lithium or a locally developed equivalent* " The Choice and Medication website is subscribed to by 46 of the 52 mental health Trusts in England plus Wales, Scotland and Northern Ireland. There are lithium resources on the website so could this be	Thank you for your comment, the guideline development group has been amended to reflect your concerns.

					reworded as: “National Patient Safety Agency’s information on lithium or a locally available equivalent “	
College of Mental Health Pharmacy	46	NICE	1.10.11	37	Please rephrase “arrange an ECG” – to “offer to arrange an ECG” – no point in arranging if the patient refuses.	Thank you for your comment, but the guideline development did not think this was appropriate given the risks involved.
College of Mental Health Pharmacy	47	NICE	1.10.13	37	“1.10.13 Consider maintaining serum lithium levels at 0.8–1.0 mmol per litre for a trial period of at least 6 months for people who: “ We would recommend this is only done with extra monitoring because: 1. Recent research on the Norfolk Lithium Database and its 12 years of longitudinal data on over 4000 patients (not available to you at the time you wrote this but now submitted for publication), shows that from 613 patients who had levels reported to be above 0.8mmol/L: “Two consecutive exposures (three months apart) of lithium levels within the range 0.81-1.2mmol/L led to a statistically significant increase in creatinine in the year following exposure. One exposure to a lithium level in the range 1.21-2.0mmol/L showed an increase in the level of creatinine in the year following exposure. This suggests that higher level lithium exposure has an additive impact on renal function, separate to exposure to lithium alone.”	Thank you for your comment. The GDG expressed concern over possible over investigation of people with lithium and were presented with evidence from a national audit that psychiatrists were not following the previous three monthly monitoring of lithium. However, the data that you have presented has persuaded the GDG to amend the recommendations on lithium to 3 monthly for the first 12 months, and then 3 monthly after the first year in patients with a last lithium level of 0.8 mmol/l and anybody with a lower lithium level with medical or mental state reasons for closer monitoring. The recommendation has been amended to reflect this.
College of Mental Health Pharmacy	48	NICE	1.10.16	38	“*Measure the person’s serum lithium level every 6 months* “ This is **inconsistent with the FULL guidelines**, which state (p238, line 15) “According to the GDG expert opinion, laboratory tests that are required specifically for people receiving long-term therapy with lithium include: - At initiation of treatment: 3 tests of serum lithium concentration in order to establish the drug’s therapeutic dose - Over 1 year: **four** tests of serum lithium concentration, two tests of renal function (urea, creatinine and electrolytes); two tests of thyroid	Thank you for your comment. Thank you for your comment. The GDG expressed concern over possible over investigation of people with lithium and were presented with evidence from a national audit that psychiatrists were not following the previous three monthly monitoring of lithium. However, the data that you have presented has persuaded the GDG to amend the recommendations on lithium to 3 monthly for the first 12 months, and then 3 monthly after the first year in patients with a last lithium level of 0.8 mmol/l and anybody with a lower lithium

					function; and two tests of calcium levels." We would strongly dispute the summary recommendation: 2. If you recommend 6-monthly, *practically* that results in every 6-9 months or longer in the community. To recommend 3 months at least results in 3 tests in a year in most people. 3. Our recent research on the Norfolk Lithium Database and its 12 years of longitudinal data on over 4000 patients (not available to you at the time you wrote this but has since been submitted for publication), shows that from 613 patients who had levels reported to be above 0.8mmol/L: "Two consecutive exposures (three months apart) of lithium levels within the range 0.81-1.2mmol/L led to a statistically significant increase in creatinine in the year following exposure. One exposure to a lithium level in the range 1.21-2.0mmol/L showed an increase in the level of creatinine in the year following exposure. This suggests that higher level lithium exposure has an additive impact on renal function, separate to exposure to lithium alone." It appears that changing the recommendation to 6-monthly from the previous 3-monthly is based on no safety evidence nor explanation and will ultimately risk harming patient's renal functions if allowed to have plasma levels in the higher range for several months. We recommending making the shorter guideline consistent with the full guideline and revert this to 3-monthly monitoring. We can send a full copy of the draft paper if you wish. We fully realise that you would not be able to incorporate this paper but suggest you note this so as not to have to change your recommendations or withdraw them when this new data appears.	level with medical or mental state reasons for closer monitoring. The recommendation has been amended to reflect this.
College of Mental Health Pharmacy	49	NICE	1.10.15	38	"1.10.15 Warn people taking lithium not to take over-the-counter non-steroidal anti-inflammatory drugs and avoid prescribing these drugs for people with bipolar disorder if possible; if they are prescribed, this should	Thank you for your comment. Regarding your first point, the guideline development group considered that the term p.r.n was widely understood and wished to maintain

					be on a regular (not p.r.n.) basis and the person should be monitored closely“ ▪ Please don’t use Latin abbreviations – better to replace brackets with…. “ (not “when required”) “ ▪ We think closely needs some explanation and perhaps an interval e.g. monthly	consistency with other guidelines that use this term. Regarding your second point, the recommendation has been redrafted to say “monthly until a stable lithium level is reached and then every 3 months”.
College of Mental Health Pharmacy	50	NICE	1.10.17	38	“Consider measuring serum lithium levels every 3 months for: - people who are at risk of renal, thyroid or other complications “ Our recent research on the Norfolk Lithium Database and its 12 years of longitudinal data on over 4000 patients (not available to you at the time you wrote this but has since been submitted for publication), shows that from 613 patients who had levels reported to be above 0.8mmol/L: “Two consecutive exposures (three months apart) of lithium levels within the range 0.81-1.2mmol/L led to a statistically significant increase in creatinine in the year following exposure. One exposure to a lithium level in the range 1.21-2.0mmol/L showed an increase in the level of creatinine in the year following exposure. This suggests that higher level lithium exposure has an additive impact on renal function, separate to exposure to lithium alone.” Thus, everyone is at risk of renal complications from even one level above 1.2. If not monitored every 3 months the risk of maintaining higher/toxic levels is significantly increased. Detection after the horse has well and truly bolted will result in unnecessary renal damage. By this line alone, NICE is in danger of failing many a patient.	Thank you for your comment. Thank you for your comment. The GDG expressed concern over possible over investigation of people with lithium and were presented with evidence from a national audit that psychiatrists were not following the previous three monthly monitoring of lithium. However, the data that you have presented has persuaded the GDG to amend the recommendations on lithium to 3 monthly for the first 12 months, and then 3 monthly after the first year in patients with a last lithium level of 0.8 mmol/l and anybody with a lower lithium level with medical or mental state reasons for closer monitoring. The recommendation has been amended to reflect this.
College of Mental Health Pharmacy	51	NICE	1.10.22	39	This advice is not appropriate if a lady is pregnant and on lithium.	Thank you for your comment, revised recommendation number 1.1.4 has been amended to state that clinicians should refer to the NICE guideline on antenatal and postnatal mental health for the treatment of pregnant women.

College of Mental Health Pharmacy	52	NICE	1.10.25	39	As per page 14 "*do not offer valproate to girls of child bearing age*". The previous guidelines used the term child-bearing potential, arrived at after much discussion. We think this statement needs to be either toned down or explained. You haven't said why, because if a girl/young woman is not sexually active or cannot have children then the concern about teratogenicity is irrelevant. Furthermore, sometimes the risk of teratogenicity with valproate may be a reasonable option and even the patients' preference compared to the significant weight gain with olanzapine, and need for detailed adherence with lithium. We suggest rephrasing (throughout) to "*Valproate can be teratogenic, therefore do not routinely offer it to women of child bearing potential unless all other options have been exhausted and on balance this risk of considered appropriate*".	Thank you for your comment, the phrasing used throughout the full guideline and the NICE guideline is 'childbearing potential'. After considering this point, the GDG decided that alternatives should be found and supported by professionals rather than exposing girls to the risk of valproate.
College of Mental Health Pharmacy	53	NICE	1.10.31	40	This advice is not appropriate if a woman is pregnant and on valproate.	Thank you for your comment, revised recommendation number 1.1.4 has been amended to state that clinicians should refer to the NICE guideline on antenatal and postnatal mental health for the treatment of pregnant women.
College of Mental Health Pharmacy	54	NICE	1.11.3	40	Suggest re-wording this slightly difficult sentence e.g. "Assessment of people with suspected bipolar disorder should be conducted in Early Intervention ~~in Psychosis~~ services."	Thank you for your comment. This recommendation has been revised. However, the term 'early intervention in psychosis service' has been retained for consistency with other guidelines.
College of Mental Health Pharmacy	55	NICE	1.11.4	41	Need to add a comment about the influence of substance misuse on presentation and diagnosis.	Thank you for your comment. The relationship between substance misuse and Bipolar Disorder is covered by the NICE guideline: Psychosis and substance misuse (NICE CG 120), which is referred to in revised recommendation number 1.1.7.
College of Mental Health Pharmacy	56	NICE	1.11.10	42	Why is it recommended to not continue antipsychotics beyond 12 weeks when treating a young person for mania? It may take longer than 12 weeks to achieve stability, particularly if the first antipsychotic used is ineffective. In many cases when an antipsychotic has	Thank you for your comment. The recommendation on aripiprazole comes from the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks

					been effective one would want to continue it as a maintenance treatment especially if there is good evidence for such use (quetiapine, olanzapine and aripiprazole are all licensed as maintenance agents in BPD and although not licensed there is good evidence that risperidone is effective in preventing manic relapse in patients who had a manic episode that responded to risperidone). And of course the manic episode may have been so harmful for the patient that stopping treatment would place the patient at significant risk from the consequences of relapse.	of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be "routinely" continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
College of Mental Health Pharmacy	57	Full	14	46	"…*it's possible*" should be "*its possible*" without an apostrophe	Thank you, it has been amended.
College of Mental Health Pharmacy	58	General	General	General	It is a threat to the worldwide credibility of NICE that published evidence is discarded by this Guidance to be replaced by opinion and assumptions about treatments and extrapolations regarding unproven therapies as first line treatments. Bipolar depression and unipolar depression cannot be assumed to be fundamentally alike and so it cannot be assumed that the same psychological therapies work for both. It only requires a look at the difference in efficacy of drug therapies for unipolar and bipolar depression to mandate this assumption be re-examined. NICE states that its guidelines are "transparent in its development, consistent, reliable and based on a rigorous development process". We are deeply concerned that this draft guideline fails these ideals. There is a huge risk that it will be seen as a consensus statement, based on the individual preferences, beliefs and interests of some of the members of the GDG, as it appears to lack the rigorous **independent** scientific analysis "based on the best evidence" mandated by NICE.	Thank you for your comments. The guideline does not assume that unipolar and bipolar depression are the same. The GDG, when considering the psychological treatments for bipolar depression, came to the view that the approach using CBT was essentially the same whether the depression was unipolar or bipolar. Please also note that we have amended recommendation 1.6.1 (NICE guideline) to make it clear that the healthcare professional should discuss with the person with bipolar disorder the possible benefits and risks of psychological interventions and monitor mood carefully for signs of mania or hypomania or deterioration of the depression symptoms. In addition, recommendation 1.6.2 makes it clear that psychological therapists working with people with bipolar depression should have training in, and experience of, working with people with bipolar disorder. The GDG have used NICE processes to develop these guidelines, and attempted to be as transparent as possible by explaining the rationale for each recommendation in the 'linking evidence to recommendations' sections within each chapter of the full guideline report.

						Furthermore, we do believe that the recommendations are based on the best available evidence.
College of Occupational Therapists	1	Full	2.6.4	46	We value the recommendation that psychosocial education group work is a valued method of intervention. However, occupational therapy was not mentioned in the list of staff who are best placed to provide this intervention. Occupational therapists have specific training in the use of group work as a therapeutic medium and therefore have the skills to facilitate psychosocial educational group work.	Thank you for your comment. The GDG would not want to be prescriptive about which professional groups should carry out such work. We would agree that occupational therapists might be suitable for such work.
College of Occupational Therapists	2	Full	2.6.4	48	We value the recommendations that recovery outcomes should be sought rather than the primary focus being upon relapse prevention. Occupational therapists are well placed to support and promote recovery outcomes, as occupational therapy assessment and goal planning are primarily focused upon identifying individual recovery goals, and working with clients to reach these goals, and already use tools to support people to identify meaningful goals.	Thank you for your comment. The GDG would not want to be prescriptive about which professional groups should carry out such work. We would agree that occupational therapists might be suitable for such work.
College of Occupational Therapists	3	Full	5.3.3	100	The list of components for assessment demonstrated clearly the benefits of multidisciplinary working (MDT). Occupational therapists are well placed in assessing social and personal functioning and current psychosocial stressors, and the possible factors associated with changes in mood, including relationships, psychosocial factors and lifestyle changes as part of that MDT.	Thank you for your comment. The GDG made recommendations that were not specific to a job title given that a range of healthcare professionals with appropriate training could conduct the assessment.
College of Occupational Therapists	4	NICE/Full	1.9.1/ 7.6.1.38	239	The guidance suggests the team place emphasis on engagement rather than risk management. Should interventions based upon self-management skills not also be included in the guidance?	Thank you for your comment. The GDG found evidence that psychological treatment approaches that encourage self-management are indeed effective in preventing relapse. However, the GDG could find no specific evidence that self-management without professional help was effective so no recommendations on such self-management have been made.
College of Occupational Therapists	5	NICE/Full	1.9.6/ 7.6.1.43	240	We value the recommendation that supported employment programmes should be offered to people with bipolar disorder who wish to find or return to work.	Thank you. This recommendation is based upon a careful evaluation of the evidence around supported employment and its

					Information on workplace support should also be included for maintaining those already in employment. It is well evidenced that Occupational Therapists are well placed to provide the type of employability support, guidance and structure that is suggested within the recommendation around other occupational or educational activities, including pre-vocational training, for people who are unable to work or unsuccessful in finding employment.	superiority over other attempts to help people with psychoses to gain employment. The guidelines do not usually specify specific professionals for specific roles or jobs, rather, we look at the interventions and the skills needed to deliver these.
Department of Health	1	General	General	General	No comments.	Thank you.
Expert Reviewer 1	1	NICE	General	General	The guidelines represent the outcomes of a systematic and thorough review process that considers bipolar disorder from a wide range of perspectives. Strengths of the guidelines include the terminology that clearly see the service-user as at the centre of their care who is 'offered' treatments and allowed information on both benefits and risks of interventions. It is comforting to see that medication regimes are to be regularly reviewed. The recommendation of both individualised psychological treatments for bipolar disorder as well as the option for recommended treatments for depression provides a realistic opportunity for service-users to receive a potentially helpful intervention.	Thank you for your comments.
Expert Reviewer 1	2	NICE	General	General	The section specifically on recovery (1.9) is very welcome, as is the suggestion that carers are made aware of recovery. However, I believe there are a number of missed opportunities in the guidelines to make patients aware of the potential recovery from their problems. Specifically, this information can be offered in primary and secondary care before or while active psychological interventions are offered. It is important that patients are provided with balanced information about both the potential future risks of their current symptoms in terms of relapse and also the potential future recovery that they may achieve, and reclaiming their lives again. It is also important that no specific message is given that recovery must rely on specific treatments. It is clear that there are many pathways to recovery that are idiosyncratic, both with	Thank you for your comment. The Guideline Development Group agrees that a focus on recovery is important, and endeavoured in its guideline to capture this as far as the evidence would allow. Recovery is given some prominence in the recommendations about carers (1.1.14, 1.1.18) and primary care (1.2.4), and the section on 'Promoting recovery and return to primary care' sets out the service context. In response to your comment, the GDG has, in addition, strengthened the first recommendation in the guideline to emphasis recovery and building relationships, and added the importance of personal recovery goals to revised recommendation 1.3.2.

					and without medication, and with and without psychological intervention, over varying periods.	
Expert Reviewer 1	3	NICE	General	General	I have not seen any specific recommendation focused on the dangers of polypharmacy and the recommendations that patients on multiple types of medication need to be reviewed regularly to allow withdrawal of some of the medication, and simplification of their regime.	Thank you. This is very helpful. Recommendation 1.10.1 has been added to address your concerns.
Global Organization for EPA and DHA Omega-3s (GOED)	1	Full	General	General	GOED commends you for considering nutritional interventions for the management of bipolar disorder. With respect to the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), GOED wishes to bring your attention to two meta-analyses that were not included in your review. While we note that many of the individual studies were considered, we recognize that the use of meta-analytic techniques often provide a different interpretation of the data. • Sarris J Mischoulon D and Schweitzer I (2012). Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. J Clin Psychiatry 73:81-6. http://www.ncbi.nlm.nih.gov/pubmed/21903025 • Grosso G Pajak A Marventano S Castellano S Galvano F Bucolo C Drago F Caraci F (2014). Role of omega-3 Fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. PLoS One 9:e96905. http://www.ncbi.nlm.nih.gov/pubmed/24805797	Thank you for this suggestion, but we did in fact cite the Sarris et al., meta-analysis in section 6.1.1. However, we chose to answer the question about nutritional interventions by conducting our own systematic review. We did not examine the Grosso et al., meta-analysis as it was published too late to be included (May 2014), and in any event, we included the same trials of bipolar disorder. Therefore, we do not believe adding this paper now would be useful.
Greater Manchester West Mental Health NHS Foundation Trust	1	NICE/Full	1.11.10/ 10.8.1.3	294	comments are: -the restriction of antipsychotic use for 12 weeks does not describe clearly whether the 12 weeks limit is relevant for an antipsychotic prescription with good adherence after having reached a therapeutic dose of an antipsychotic, tolerated well by young person, which is seen as successful in managing manic/hypomanic symptoms or not -Due to higher risk of side effects in youth from antipsychotic medications, limitations of using	Thank you for your comment. The GDG recognised the growing evidence of harms associated with antipsychotics, especially those in most common use at the time of writing (olanzapine, quetiapine etc) which are strongly associated with metabolic syndromes such as diabetes. However, given the lack of evidence regarding the efficacy of any pharmacological treatment of bipolar disorder in children and young people, the GDG

					Valproate, and Lithium advised only as second line treatment in this guidance, it is quite likely that achieving a therapeutic dose of a relatively well tolerated antipsychotic medication may take some time notwithstanding the issue of compliance especially when treating as outpatients. -The restriction of 12 weeks also does not specify any exceptions where patient may not show a good response/recovery from hypomania/mania within first 12 week treatment. -Advice of using Lithium as second line and antipsychotics as fist line appears not to be well supported by limited evidence available for either which reminds of similar prescribing advice for psychosis in adults and young people, revised more recently (2007 guidance) as currently based on choosing a suitable medication after individual discussion with patients on side effects, tolerance and compliance instead	therefore decided to extrapolate from the adult data, which prioritises antipsychotics over lithium and valproate for acute mania. Because bipolar disorder is a relapsing and remitting condition that rarely becomes chronic, the use of antipsychotics is bound to be needed for shorter amounts of time than in people with schizophrenia where psychotic episodes are longer and become chronic. The only drug licenced is aripiprazole, which is the subject of a technology appraisal, and both the licence and the TA limit the use of aripiprazole to 12 weeks. However, we do take your point that sometimes antipsychotics are needed for longer than 12 weeks, and have therefore amended the recommendation to say that drug treatment should not 'routinely' continue for longer than 12 weeks, and that at 12 weeks there should be a multidisciplinary review to assess whether to continue treatment.
Greater Manchester West Mental Health NHS Foundation Trust	2	NICE/Full	1.11.15/ 10.8.1.8	295	Comments: -When treating moderate to severe depression not responsive/not engaging with psychological treatment or severe suicidal risk not responsive to psychological treatment effectively requiring antidepressant treatment with an antipsychotic, restriction of 12 weeks appears to contradict the earlier NICE advise of treating a severe episode of depression for at least 6 months on the therapeutic dose effective for the patient and tolerated well by them.	Thank you for your comment, with which the Guideline Development Group has some sympathy. While the group wishes to restrict the use of antipsychotic medication in young people because of the limited evidence for efficacy and the evidence of side effects, it recognises that for some young people antipsychotics may need to be continued. The recommendation has therefore been changed to say 'do not routinely continue antipsychotic treatment for longer than 12 weeks.' and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
Greater Manchester West Mental Health NHS Foundation Trust	3	Full	1.11.16/ 10.8.1.9	296	Comments: -Long term management of Bipolar disorder with psychological interventions for youth does not consider youth with persisting symptoms and impairment of functioning who may be unresponsive to or not able to engage with psychological therapy to maintain recover	Thank you for your comment, but the evidence is limited in this area and the guideline development group considered that children and young people who were not responsive to psychological therapy would not be maintained on it for long-term treatment. Clinicians would

					-Neither does this describe options for management of patients with repeated episodes or rapid cycling disorder	only know if there was a response to psychological treatment if the child or young person was acutely ill and symptomatic. The reviews undertaken for this guideline update did not indicate that rapid cycling disorder should be treated any differently from other types of bipolar disorder (see revised recommendation number 1.1.8).
International Society for Psychological and Social Approaches to Psychosis (UK branch)	1	NICE	1.1.6	16	No mention here of guidelines on psychosis and schizophrenia in adults or young people – it seems an important omission.	Thank you for your comment. The recommendation is for people with bipolar disorder and comorbidities. If a person has symptoms of schizophrenia and bipolar they would be diagnosed with schizoaffective disorder, which is covered by the psychosis and schizophrenia guideline (NICE CG178).
International Society for Psychological and Social Approaches to Psychosis (UK branch)	2	NICE	1.1.19	19	The potential intergenerational effects of parental mental illness receive limited attention, so this item is very welcome. However could the last bullet point be expanded to be more specific, considering what types of support might be relevant for children and young people, and what help might be offered to parents with bipolar disorder to support them in parenting.	Thank you for your comment. The GDG considered that there was such a wide range of potential scenarios involving intergenerational effects of parental mental illness that such detail would be inappropriate for a recommendation. Instead a more general recommendation to provide such support has been made.
International Society for Psychological and Social Approaches to Psychosis (UK branch)	3	NICE	1.3.12	22	As many specific areas of assessment are mentioned, it seems striking that there is no mention of the value of including in assessment a personal history which attends to early childhood adversity, attachment issues, trauma etc. Many patients see such issues as highly relevant to their mental health problems, and feel poorly understood when they are not addressed. Not addressing them may have an adverse impact on the therapeutic alliance and be a missed opportunity for supporting people in making sense of their difficulties, which can itself be therapeutic. This is an addition to the accumulating research evidence of the relevance of such factors. Might it be helpful to specify that the aim of assessment is not just a diagnosis but a formulation of the person's problems.	Thank you for your comment. 1.3.2 refers to assessment not purely a diagnosis. It refers to a full psychiatric assessment including psychosocial factors affecting current and past symptoms and function. The GDG considered that there were numerous factors to consider in the assessment and that it was not possible to spell out every factor that might be important in every person with suspected bipolar disorder. However, we have received a number of comments such as yours in relation to developmental issues so development of the disorder over the lifespan has been added to recommendation 1.3.2.

International Society for Psychological and Social Approaches to Psychosis (UK branch)	4	NICE	1.9	33	Perhaps unintentionally the guideline comes across as taking a rather narrow view of recovery. For example more attention might be given to the impact of illness on self-image and agency, and on relationships, and the potential value of services offering support with these areas. There would seem to be arguments here for adding a statement equivalent to that in the psychosis and schizophrenia in adults guideline, that psychodynamic and principles may be used to understand the experience and relationships of people with bipolar disorder.	Thank you for your comment. The Guideline Development Group agrees that a focus on recovery is important, and endeavoured in its guideline to capture this as far as the evidence would allow. Recovery is given some prominence in the recommendations about carers (revised recommendation number 1.1.14, 1.1.18) and primary care (1.2.4), and the section on 'Promoting recovery and return to primary care' sets out the service context. In recommendation 1.9.4, the first bullet point makes reference to 'individualised social and emotional recovery goals' which encompasses some of the examples you raise, such as self-image and agency. In response to your comment, the GDG has, in addition, strengthened recommendation 1.1.1 in the guideline to emphasis recovery and building relationships, and added the importance of personal recovery goals to revised recommendation 1.3.2.The GDG disagree with the suggestion that psychodynamic principles can be used to understand people with bipolar disorder.
International Society for Psychological and Social Approaches to Psychosis (UK branch)	5	NICE	1.9.2	33	Patients frequently comment on the impact of repeated changes in the practitioners working with them and being unable to develop a sustained relationships – is it possible for this to be addressed in the guideline.	Thank you for your comment, this is addressed in the guideline on service user experience in adult mental health (NICE CG136) – which is meant to be read alongside this guideline.
International Society for Psychological and Social Approaches to Psychosis (UK branch)	6	NICE	1.5.2 (to 1.5.10)	24 25	It would be helpful for the guidance to include comment on the use of benzodiazepines.	Thank you for your comment. The main use of benzodiazepines for people with bipolar will be in the management of challenging behaviour and violence. This will be covered in the forthcoming guideline on the management of violence and aggression. Recommendation 1.4.3 has been amended to include a cross reference to this guideline.
International Society for	7	NICE	1.10.22 1.10.23	39	It would be helpful for the guidance to include comment on stopping antipsychotics and mood	Thank you for your comment. The guideline already includes recommendations on starting,

Psychological and Social Approaches to Psychosis (UK branch)					stabilisers other than lithium.	monitoring and stopping valproate and the guideline development group has now included advice on how to start, monitor and stop lamotrigine, and stopping antipsychotics.
International Society for Psychological and Social Approaches to Psychosis (UK branch)	8	Full	8.3.2	259	Only structured therapies have been considered. There is case report evidence that other interventions may be helpful at least to some individuals eg. peer support, and unstructured therapies. Widening research aspirations would allow the possibility of reaching a position where there is a wider range of choices	Thank you for your comment. It is very difficult to establish if an intervention does more good than harm based on case report evidence. There are two major issues. First, it is nearly impossible to find all case reports, and it is very unlikely that those that are published (or available) are representative of all reports. Second, without some type of control group it is difficult to establish if the intervention was the reason for any change in outcome. Therefore, insufficient evidence was found on the effectiveness of other forms of psychological support, including peer support, to warrant a recommendation.
International Society for Psychological and Social Approaches to Psychosis (UK branch)	9	Full	8.3.2	259	Section 8.2 earlier refers to the limitations in the evidence about long term and broader quality of life outcomes of recommended treatments. In view of this, investigation of this should surely be a priority. This is particularly in view of emerging evidence that longer term outcomes for antipsychotics may be less positive than previously thought (eg. see Wunderink 2013)	Thank you for your comment, we agree with your concerns. Research recommendation 8.3.2.1 explicitly refers to quality of life and recovery outcomes. In research recommendations 8.3.2.2 and 8.3.2.3 'clinical and cost effectiveness' would include the outcomes you refer to.
International Society for Psychological and Social Approaches to Psychosis (UK branch)	10	General	General	General	Please see comment 4 above. The first point here applies to the guideline generally.: Perhaps unintentionally the guideline comes across as taking a rather narrow view of recovery. For example more attention might be given to the impact of illness on self-image and agency, and on relationships, and the potential value of services offering support with these areas.	Thank you for your comment. The Guideline Development Group agrees that a focus on recovery is important, and endeavoured in its guideline to capture this as far as the evidence would allow. Recovery is given some prominence in the recommendations about carers (revised recommendation number 1.1.14, 1.1.18) and primary care (1.2.4), and the section on 'Promoting recovery and return to primary care' sets out the service context. In recommendation 1.9.4, the first bullet point makes reference to 'individualised social and emotional recovery goals' which encompasses some of the examples you raise, such as self-image and agency. In response to your

						comment, the GDG has, in addition, strengthened recommendation 1.1.1 in the guideline to emphasis recovery and building relationships**,** and added the importance of personal recovery goals to revised recommendation 1.3.2.
International Society for Psychological and Social Approaches to Psychosis (UK branch)	11	General	General	General	It would be helpful for the guideline to more specifically address the issue of choice in relation to therapy. For example, people who do not have access to the recommended structured therapies, or who have not found these helpful, or want help with issues such as relationships which might be equally well be addressed by other forms of psychological support eg. systemic or psychodynamic approaches, or peer support. Generally there seems to be very minimal attention to the potential value of peer support.	Thank you for your comment, revised recommendation numbers 1.2.5 and 1.6.1 have been amended to include personal preference when discussing therapies. Insufficient evidence was found on the effectiveness of other forms of psychological support, including peer support, to warrant a recommendation.
Lancashire Care NHS Foundation Trust	1	General (both)	General	General	*NICE guideline: sections 1.2.5, 1.6.1, 1.11.12* *Full guideline: pages 148, 256* The recommendations for the use of psychological treatments recommended in the (unipolar) depression guidance contradicts the statement in the FULL guideline (p48, lines 5-6) that "the treatment offered is likely to be generic and lacks an evidence base for this condition" The argument in the FULL guidance (p256) that the quality of evidence for unipolar psychological interventions is higher than for bipolar does not (in our view) justify the assumption that unipolar interventions are safe and effective for a bipolar population - this would require additional evidence that interventions for one condition could be applied to another condition. Indeed this assumption runs counter to theoretical models that suggest mania may be triggered by actions intended to avoid depression - e.g. Abraham, 1911, Neale, 1988; Lyon et al, 1999; Mansell et al, 2007) We agree with the recommendation that psychological interventions should be conducted by psychological therapists who have training and expertise in working with people with bipolar disorder". Such therapists should to be able to deliver evidence-based bipolar-	Thank you for your comment. The sentence on page 48 relating to 'lack of an evidence base' has been removed because it was misleading. The GDG noted that the evidence for psychological interventions for unipolar depression is consistent with the evidence for bipolar depression and of much higher quality, and therefore the use of interventions for unipolar were deemed appropriate for this population. The GDG did carefully consider the concerns that you raised but concluded there are a number of factors which are thought to lead to 'switching' from depression to mania, such as the use of SSRIs or psychological therapies. The GDG came to the conclusion that people with bipolar depression should be given the choice once possible benefits and risks are explained. In addition, (as you noted) a recommendation was made that professionals treating people with Bipolar Disorder should be trained and experienced in doing so (see recommendation 1.2.6 and 1.6.2). All treatments have a risk of side effects

					specific psychological treatments, so it is unclear why these therapists would opt to provide generic/unipolar interventions instead. Also, the potential risk that depression-focused interventions (e.g. behavioural activation) may trigger mania or hypomania requires careful consideration.	– the recommendations balance the risks and benefits of these treatments, as should clinicians in each case. The recommendation (1.6.1) was amended to include advice that healthcare professionals should monitor mood carefully and if there are signs of hypomania or deterioration of the depressive symptoms, liaise with or refer the person to secondary care. If the person develops mania or severe depression, refer them urgently to secondary care.
Lancashire Care NHS Foundation Trust	2	NICE	1.7.3	12	We support this recommendation for the use of bipolar-specific psychological interventions to prevent/reduce relapse risk and address residual difficulties.	Thank you for your comment.
Lancashire Care NHS Foundation Trust	3	NICE	1.3.1	22	NICE guideline: sections 1.3.1, 1.3.5 (pages 22,23) Full guideline: page 224 Whilst Early Intervention services are well placed to support a normalising, recovery focused and youth-friendly assessment of people with a suspected first episode, there are likely to be resource implications for EI services that are typically only funded to work with caseloads based on population estimates of the incidence of psychoses, so accepting all cases of suspected bipolar (including bipolar 2 and bipolar 1 without psychotic features) is likely to require changes to commissioning arrangements as well as service entry criteria to respond to increased demand. Early Intervention services are commissioned to accept referrals from people aged 14-35, so they would not be appropriate for people who require assessment and treatment but are outside of these age parameters (whether because of late onset or long duration of unrecognised/undiagnosed bipolar symptoms).	Thank you for your comment. The psychosis and schizophrenia guideline looked at the evidence underpinning the use of EIS services for people with suspected and early psychosis. These populations include people who later develop schizophrenia, bipolar disorder and other psychoses. All the trials included were with mixed populations. We accept that schizophrenia and bipolar are different conditions, with different guidelines. However, there is considerable overlap in the treatment and management of these conditions. It is also important that, for both groups access to a service that works on the principle of early intervention is important. The GDG does however concede that there is some variation in service provision, and has therefore revised the recommendation to set out the components of the teams that should provide assessment for bipolar disorder, rather than stating that the team must be EIS. Recommendation 1.3.5 has been merged with revised recommendation 1.3.1.
Lancashire Care NHS Foundation Trust	4	NICE	1.7.1	29 30	The recommended content of discussion appears very medically focused and could be substantially improved by being a) based on individual needs, b) recovery	Thank you. The recommendation is meant to focus on a discussion about long term treatment, which will be about psychological

					focused (ie optimistic & empowering, paying attention to wellbeing and psychosocial functioning rather than simply symptom management and relapse prevention), c) decatastrophising (in light of the theoretical possibility that mood instability may be exacerbated by fear of relapse, cf Mansell et al, 2007).	and drug treatments. The whole guideline is to be read in conjunction with the Service User Experience in adult mental health guideline which is very patient and need focussed. There is, in addition, a section on recovery (1.9) and the importance of personal recovery goals has been added to revised recommendation 1.3.2.
Lancashire Care NHS Foundation Trust	5	NICE	1.7.2 (to 1.7.4)	30 31	We support these recommendations although most healthcare providers are likely to struggle to meet demand if such interventions are offered to all people with bipolar disorder. In order to maximise the likelihood that providers will work towards increasing capacity to deliver these interventions, it would be helpful if the recommendations stated unequivocally that they should be offered to all service users (or all families/carers where applicable).	Thank you. The recommendations do say offer people with bipolar. The GDG did not see the need to add in all people as there are no exceptions in the recommendations.
Lancashire Care NHS Foundation Trust	6	Full	2.2.6	32	*Full guideline: page 32* Whilst the FULL guideline acknowledges the literature on trauma (and particularly childhood trauma) in the lives of many people with bipolar disorder, we were unable to find any recommendations in the NICE guidance on a) assessment and formulation of the potential role of trauma in making sense of bipolar presentations (including assessing current risks, as well as safeguarding), b) treatment recommendations (even if simply a reference to the PTSD guidance), and c) research recommendations (e.g. development and evaluation of psychological interventions for comorbid PTSD and bipolar).	Thank you for your comments. Revised recommendation 1.3.2 on the assessment of people with suspected bipolar disorder makes reference to the consideration of psychosocial factors with reference to both current mood and past episodes. We would expect secondary care mental health professionals to be aware that trauma may be a relevant factor to consider. However, we have received a number of comments that asked us to consider developmental issues over the lifespan which has been added to revised recommendation 1.3.2. These might include trauma as well as other issues. The issue of safeguarding is covered in revised recommendation 1.1.19. It is not possible to make recommendations in every clinical scenario, and the GDG considered other recommendations to have greater priority.
Lancashire Care NHS Foundation Trust	7	Full	2.1.1 2.5		Distinction between Bipolar I and II – It would be helpful to add some discussion on whether Bipolar II patients switch to Bipolar I, and the frequency, predictors, subsequent course etc. The stability of	Thank you for your comments. The introduction is not intended to be a definitive textbook and this is an issue of contention and considerable uncertainty. For these reasons

					Bipolar II diagnoses is a matter of considerable concern to many patients who have concerns about deterioration to more severe disorder	we do not think it is appropriate to go into such detail.
Lancashire Care NHS Foundation Trust	8	Full	2.3.4	37	Assessment – Diagnosis. This section does not consider Smith DJ et al, 'Unrecognised bipolar disorder in primary care patients with depression' BJP July 2011 199:49-56. This study assessed the validity of HCL-32 and Bipolar Spectrum Diagnostic Scale questionnaires in detection of cases of bipolar disorder.	Thank you for your comment. Unfortunately the study that you quote did not utilise an adequate assessment tool for the diagnosis of bipolar disorder so the guideline was unable to consider it.
Lancashire Care NHS Foundation Trust	9	General (both)	General	General	The emphasis in management of bipolar disorder should be on promotion of long term recovery. The flow of the text of both documents diminishes the importance of long term management in first dealing extensively with acute episodes before moving to discuss long term management. Unfortunately, this creates the perception of long term management as an afterthought. This could be remedied by re-ordering the sections of the guidance placing the sections relating to long term management near to the start of the text. This is important in promoting shift in the strategic management of patients with bipolar disorders away from intermittent episodic models towards long term multidisciplinary condition management across the changing phases of the disorders.	Thank you for your comment. While the guideline development group has some sympathy with the points you have raised, it does not feel that restructuring the guideline in the way you have suggested will be helpful for clinicians. In its current form the guideline is ordered as far as possible to correspond to a care pathway (diagnosis, assessment, treatment for acute episodes, long-term treatment and promoting recovery) for a person with a first presentation for whom treatment for the acute episode would be prioritised before discussion of long-term treatment**.**
Lancashire Care NHS Foundation Trust	10	NICE	1.3.12	22	As many specific areas of assessment are mentioned, it seems striking that there is no mention of the value of including in assessment a personal history which attends to early childhood adversity, attachment issues, trauma etc. Many patients see such issues as highly relevant to their mental health problems, and feel poorly understood when they are not addressed. Not addressing them may have an adverse impact on the therapeutic alliance and be a missed opportunity for supporting people in making sense of their difficulties, which can itself be therapeutic. This is an addition to the accumulating research evidence of the relevance of such factors. Might it be helpful to specify that the aim of	Thank you for your comment. 1.3.2 refers to assessment not purely a diagnosis. It refers to a full psychiatric assessment including psychosocial factors affecting current and past symptoms and function. The GDG considered that there were numerous factors to consider in the assessment and that it was not possible to spell out every factor that might be important in every person with suspected bipolar disorder. However, we have received a number of comments such as yours in relation to developmental issues so development of the disorder over the lifespan has been added to recommendation 1.3.2.

					assessment is not just a diagnosis but a formulation of the person's problems.	
Lancashire Care NHS Foundation Trust	11	NICE	1.9	33	Perhaps unintentionally the guideline comes across as taking a rather narrow view of recovery. For example more attention might be given to the impact of illness on self-image and agency, and on relationships, and the potential value of services offering support with these areas. There would seem to be arguments here for adding a statement equivalent to that in the psychosis and schizophrenia in adults guideline, that psychodynamic and principles may be used to understand the experience and relationships of people with bipolar disorder.	Thank you for your comment. The Guideline Development Group agrees that a focus on recovery is important, and endeavoured in its guideline to capture this as far as the evidence would allow. Recovery is given some prominence in the recommendations about carers (revised recommendation number 1.1.14, 1.1.18) and primary care (1.2.4), and the section on 'Promoting recovery and return to primary care' sets out the service context. In recommendation 1.9.4, the first bullet point makes reference to 'individualised social and emotional recovery goals' which encompasses some of the examples you raise, such as self-image and agency. In response to your comment, the GDG has, in addition, strengthened recommendation 1.1.1 in the guideline to emphasis recovery and building relationships, and added the importance of personal recovery goals to revised recommendation 1.3.2.The GDG disagree with the suggestion that psychodynamic principles can be used to understand people with bipolar disorder.
Lancashire Care NHS Foundation Trust	12	NICE	1.9.2	33	Patients frequently comment on the impact of repeated changes in the practitioners working with them and being unable to develop a sustained relationships – is it possible for this to be addressed in the guideline.	Thank you for your comment, this is addressed in the guideline on service user experience in adult mental health (NICE CG136) – which is meant to be read alongside this guideline.
Lancashire Care NHS Foundation Trust	13	NICE	1.5.2 (to 1.5.10)	24 25	It would be helpful for the guidance to include comment on the use of benzodiazepines.	Thank you for your comment. The main use of benzodiazepines for people with bipolar will be in the management of challenging behaviour and violence. This will be covered in the forthcoming guideline on the management of violence and aggression. Recommendation 1.4.3 has been amended to include a cross reference to this guideline.

Lancashire Care NHS Foundation Trust	14	NICE	1.10.22 1.10.23	39	It would be helpful for the guidance to include comment on stopping antipsychotics and mood stabilisers other than lithium.	Thank you for your comment. The guideline already includes recommendations on starting, monitoring and stopping valproate and the guideline development group has now included advice on how to start, monitor and stop lamotrigine, and stopping antipsychotics.
Lancashire Care NHS Foundation Trust	17	General	General	General	Please see comment 4 above. The first point here applies to the guideline generally: The recommended content of discussion appears very medically focused and could be substantially improved by being a) based on individual needs, b) recovery focused (ie optimistic & empowering, paying attention to wellbeing and psychosocial functioning rather than simply symptom management and relapse prevention), c) decatastrophising (in light of the theoretical possibility that mood instability may be exacerbated by fear of relapse, cf Mansell et al, 2007).	Thank you for your comment. The Guideline Development Group agrees that a focus on recovery is important, and endeavoured in its guideline to capture this as far as the evidence would allow. Recovery is given some prominence in the recommendations about carers (revised recommendations 1.1.14, 1.1.18) and primary care (1.2.4), and the section on 'Promoting recovery and return to primary care' sets out the service context. In response to your comment, the GDG has, in addition, strengthened recommendation 1.1.1 in the guideline to emphasis recovery and building relationships, and added the importance of personal recovery goals to revised recommendation 1.3.2.
Lancashire Care NHS Foundation Trust	18	General	General	General	It would be helpful for the guideline to more specifically address the issue of choice in relation to therapy. For example, people who do not have access to the recommended structured therapies, or who have not found these helpful, or want help with issues such as relationships which might be equally well be addressed by other forms of psychological support eg. systemic or psychodynamic approaches, or peer support. Generally there seems to be very minimal attention to the potential value of peer support.	Thank you for your comment, revised recommendation numbers 1.2.5 and 1.6.1 have been amended to include personal preference when discussing therapies. Insufficient evidence was found on the effectiveness of other forms of psychological support, including peer support, to warrant a recommendation.
Lancashire Care NHS Foundation Trust	19	Full	2.6.2	45 line21 (to 30)	Tier 4 admission should also be considered for complex presentations where diagnosis is unclear	Thank you for your comment. The GDG did not wish to specify that admission should be used to diagnose complex presentations because there are many considerations in relation to hospital admission. Such decisions should rest with tier 4 services.
Lancashire Care	20	Full	10.1	273 line	Further clarity on the status of lithium would be helpful	Thank you for your comment. This is an

NHS Foundation Trust				34	– the SPC states that it is not recommended in under 12s, implying that it can be prescribed in those 12 and over.	unusually difficult area, depending upon the brand of lithium used. Priadel tablets, Priadel liquid, Li-Liquid and Camcolit tablets are only licensed for 18 years upward. The only preparation that does have a license from age 12 upwards is Liskonum tablets. The BNFc lists Camcolit as well as Liskonum as options in 12 years and above despite only one of them being licensed. It is not clear why Camcolit is listed as an option for children, but the manufacturer of Camcolit has previously confirmed that it is definitely *not* licensed in this age group. The manufacturer was unsure why the BNF has not indicated the fact that it is not licensed as there is usually a statement to that effect when they include drugs without licenses. The statement has therefore been modified to say that *some* preparations of lithium are licensed for use in those over 12 years.
Lancashire Care NHS Foundation Trust	21	Full	10.1	274 line 36 (to 38)	The statement on fish oils could be more circumspect – it implies effectiveness in a range of disorders.	Thank you for your comment, we agree and the statement has been modified, omitting reference to wider use.
Lancashire Care NHS Foundation Trust	22	Full	10.7.2	293 line19 (to 22)	Although it is important to minimise use of AAPs due to adverse effects, the statement that they can only be used for 12 weeks is extremely concerning. This does not take into consideration the relatively rare but very serious, high risk cases of adolescent BP that are admitted to inpatient units, who are often difficult to treat. These YP often need trials of different AAPs in order to establish the best risk/benefit profile for each YP. They may also have chronic relapsing conditions, and each relapse may be associated with high risk suicide attempts and other risks such as vulnerability to sexual exploitation. In these cases the benefits of longer-term medication often outweighs the risks. Even within this draft , the expert opinion is quoted from the aripiprazole appraisal (pg 283) which states that the average duration of AAP treatment in YP can reach 12 months (and in rare cases possibly longer). Thus these	Thank you for your comment. The recommendation on aripiprazole comes from the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be “routinely” continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.

					recommendations ignore this expert opinion and also discriminate against young people with a serious disorder. In addition, this time limit is not stipulated in the psychosis guidelines, hence this draft is at odds with other expert opinion. Research also suggests that affective disorder is a leading cause of suicide in YP and that these cases are undertreated (Windfuhr JCPP 2008).	
Lancashire Care NHS Foundation Trust	23	Full	10.7.2	294line 17	The statement that there is no evidence of long-term benefit is based on the fact that there is very little available evidence base; this does not necessarily mean that some YP may not benefit from longer term treatment. The draft acknowledges that there may be some YP who may benefit from longer term treatment ('most' not 'all' is used in line 21), but then goes on to categorically state that long-term treatment should not be used. In light of the comments above, it would be helpful if this statement could be re-considered.	Thank you for your comment. The GDG still do not believe that pharmacological interventions should be used for the long-term management of bipolar disorder in children and young people based on the current evidence base. The recommendation on aripiprazole comes from the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be "routinely" continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
Lancashire Care NHS Foundation Trust	24	Full	10.7.4	295 line 11 (to 20)	Again, this draft is incongruent with the guidance on psychosis which states that there is a high risk of relapse if AAPs are stopped within 1-2 years of an episode. This sends a very confusing and contradictory message to clinicians and service users: if there is a BP episode with psychosis, then AAPs can be used for up to 2 yrs but only for 12 weeks without psychosis, although the risk of adverse effects is the same.	Thank you for your comment. The GDG recognised the growing evidence of harms associated with antipsychotics, especially those in most common use at the time of writing (olanzapine, quetiapine etc) which are strongly associated with metabolic syndromes such as diabetes. However, given the lack of evidence regarding the efficacy of <u>any</u> pharmacological treatment of bipolar disorder in children and young people, the GDG therefore decided to extrapolate from the adult data, which prioritises antipsychotics over

						lithium and valproate for acute mania. Because bipolar disorder is a relapsing and remitting condition that rarely becomes chronic, the use of antipsychotics is bound to be needed for shorter amounts of time than in people with schizophrenia where psychotic episodes are longer and become chronic. The only drug licenced is aripiprazole, which is the subject of a technology appraisal, and both the licence and the TA limit the use of aripiprazole to 12 weeks. However, we do take your point that sometimes antipsychotics are needed for longer than 12 weeks, and have therefore amended the recommendation to say that drug treatment should not 'routinely' continue for longer than 12 weeks, and that at 12 weeks there should be a multidisciplinary review to assess whether to continue treatment.
Lancashire Care NHS Foundation Trust	25	NICE/Full	1.11.11.10/ 10.8.1.3	296	See above: Again, this draft is incongruent with the guidance on psychosis which states that there is a high risk of relapse if AAPs are stopped within 1-2 years of an episode. This sends a very confusing and contradictory message to clinicians and service users: if there is a BP episode with psychosis, then AAPs can be used for up to 2 yrs but only for 12 weeks without psychosis, although the risk of adverse effects is the same.	Thank you for your comment. There is very little evidence regarding the efficacy of any antipsychotic treatment of bipolar disorder in children and young people. However, there is growing evidence of the harms associated with the antipsychotics, especially those in most common use at the time of writing (olanzapine, quetiapine etc) which are strongly associated with metabolic syndromes such as diabetes. Because bipolar disorder is a relapsing and remitting condition that rarely becomes chronic, the use of antipsychotics is bound to be needed for shorter amounts of time than in people with schizophrenia where psychotic episodes are longer and become chronic. The only drug licenced is aripiprazole, which is the subject of a technology appraisal, and both the licence and the TA limit the use of aripiprazole to 12 weeks. However, we do take your point that sometimes antipsychotics are needed for longer than 12 weeks, and have therefore amended the recommendation by adding the

						word ‘routinely’.
Lancashire Care NHS Foundation Trust	26	Full	1.11.15/ 10.8.1.8	296	This recommendation takes no consideration of levels of severity and ability to engage with psychological treatment; in severe high risk cases of depression often YP struggle to engage in psychological treatment and may need a pharmacological intervention much sooner than after several months of attempted psychological treatment.	Thank you for your comment. The Guideline Development Group believes the wording in recommendations 1.11.12 and 13 was misleading therefore it has been clarified. The intention was not to suggest that medication should not be considered until after 3 months of psychological therapy. The group thinks the confusion may have arisen because it states 4 to 6 *sessions* rather than 4 to 6 *weeks*. This has been rectified. The Guideline Development Group agrees that risk needs to be considered and have therefore added a recommendation to take this into account.
Lancashire Care NHS Foundation Trust	28	Full	10.1	274 line 19 (to 23)	It should be noted that this guidance is out of date, is currently being reviewed and recent Cochrane meta-analyses provide a more up-to-date review of the evidence for treatment (eg Cox; Hetrick 2012)	We accept the view expressed, however, this is the guidance currently in practice. Reference is now made to the more up-to-date Cochrane review (Hetrick et al., 2012).
Lonsdale Medical Centre	1	Full	2.1.1	21	Re: Lines 10-12 *‘Furthermore the bipolar spectrum, apart from bipolar I and bipolar II disorder, does not form part of the scope for this guideline and recommendations on its management will not be made’.* In clinical practice, patients with possible ‘cyclothymia’ and ‘soft’/subthreshold bipolar illness are often encountered and some Psychiatrists use these diagnostic labels routinely. Indeed, some of these patients seem to be treated with mood stabilisers, despite a lack of clear evidence of benefit. Therefore, and whilst appreciating that this area is not well defined, it would be helpful if the guidelines did discuss these issues in greater detail, rather than stating that they do not form part of the scope of the guideline.	Thank you for your comment. ‘Cyclothymia’ and ‘soft’/subthreshold bipolar’ were outside the scope of this guideline.
Lonsdale Medical Centre	2	Full	5.5.2/ 5.6.1.1/ 5.6.1.2/ 5.6.1.3	107	I have recently published a structured, pragmatic diagnostic decision tree for Primary Care and wonder if this may be of use in the guidelines. I attach a version of this, with references, along with several innovative figures.	Thank you for your comment and sharing your work. Mood diaries and scales are indeed tools that health professionals should consider. However, they are not appropriate or suitable in every person with suspected bipolar

					Suggested Figures for NICE guidelines.d The decision tree addresses the real-life scenarios that GPs face in the surgery, with patients who may have unrecognised Bipolar Disorder, who may present with e.g. anxiety, relationship issues and anger management problems. Watchful waiting and interim management are emphasized, as is referral for a second opinion if the diagnosis remains unclear. *'Do not use questionnaires in primary care to identify bipolar disorder in adults'.* Whilst acknowledging that Mood Questionnaires are not diagnostic, in practice they can be a useful aide-memoire and help *structure the consultation* to look for previous symptoms of mania or hypomania and help guide the need for referral at that point, or subsequently. I wonder therefore, if the wording might be changed to reflect this?	disorder so the GDG has decided not to require them in every assessment.
Lonsdale Medical Centre	3	NICE/Full	1.5.2/ 6.6.1.2	171 172	A note/suggestion about allopurinol for treatment-resistant mania. Several studies have suggested a therapeutic role for allopurinol, especially as the risks of taking allopurinol are far less than antipsychotics, as covered by Machado-Viera and the Hirota metanalysis below. Whilst acknowledging that the evidence base is still limited (and I appreciate therefore that you may feel this is excluded from the guidelines) in clinical practice (working closely with Consultant Colleagues) we have encountered a dramatic response to allopurinol 300mg tds – maintained now for over 18 months - in a 40 yr old man with resistant mania despite high dose lithium + 3000mg valproate + 1200mg quetiepine + 47.5mg olanzapine + lorazepam. With adjunctive allopurinol, the patient was able to stop quetiepine and lorazepam and reduce olanzapine to 27.5-30mg. -> Could allopurinol be mentioned as a possible option in resistant mania?	Thank you. There are a number of small RCTs in mania of medicines with novel mechanisms of action. These include medicines as diverse as allopurinol and tamoxifen. The GDG considered that the evidence for these medicines was not strong enough to support a recommendation regarding routine use in the NHS. It is acknowledged that such approaches may be appropriate in individual patients but the responsibility is with the prescriber to familiarize themselves with the primary evidence supporting efficacy and tolerability, discuss the off-label and experimental nature of the treatment to the patient and to ensure any prescribing is part of a time-limited individual treatment plan with clear monitoring of target symptoms and tolerability.

					Akhondzadeh, S., Milajerdi, M. R., Amini, H., & Tehrani-Doost, M. (2006). Allopurinol as an adjunct to lithium and haloperidol for treatment of patients with acute mania: a double-blind, randomized, placebo-controlled trial. Bipolar Disorders, 8(5 Pt 1), 485–9. doi:10.1111/j.1399-5618.2006.00363.x Fan, A., Berg, A., Bresee, C., Glassman, L. H., & Rapaport, M. H. (2012). Allopurinol augmentation in the outpatient treatment of bipolar mania: a pilot study. Bipolar Disorders, 14(2), 206–10. doi:10.1111/j.1399-5618.2012.01001.x Hirota, T., & Kishi, T. (2013, September 1). Adenosine hypothesis in schizophrenia and bipolar disorder: A systematic review and meta-analysis of randomized controlled trial of adjuvant purinergic modulators. Schizophrenia Research. Elsevier. Retrieved from http://linkinghub.elsevier.com/retrieve/pii/S0920996413003381?showall=true Machado-Vieira, R., Soares, J. C., Lara, D. R., Luckenbaugh, D. A., Busnello, J. V, Marca, G., … Kapczinski, F. (2008). A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents	
Lonsdale Medical Centre	4	Full	1.2.7-1.2.8/ 7.6.1.45 - 7.6.1.46	240	'Do not start Lithium/valproate in Primary Care' Some GPs have significant expertise in Psychiatry and Psychopharmacology. In practice, a telephone discussion with a Consultant Psychiatrist may confirm the GPs suggested management plan. Therefore, perhaps the statement could be reworded ''Do not start Lithium/valproate in Primary Care except where appropriate expertise exists and after discussion with a Psychiatrist'.	Thank you, the GDG considered your comment but came to the decision that valproate should only be started in secondary care at any point. They did however agree that lithium could be restarted in primary care and have amended recommendation 1.2.7 to reflect this.
Lonsdale Medical Centre	4	Full	1.2.7-1.2.8/ 7.6.1.45 - 7.6.1.46	240	'Do not start Lithium/valproate in Primary Care' Some GPs have significant expertise in Psychiatry and Psychopharmacology. In practice, a telephone discussion with a Consultant Psychiatrist may confirm the GPs suggested management plan. Therefore, perhaps the statement could be reworded ''Do not start Lithium/valproate in Primary Care except where appropriate expertise exists and after discussion	Thank you, the GDG considered your comment but came to the decision that valproate should only be started in secondary care at any point. They did however agree that lithium could be restarted in primary care and have amended recommendation 1.2.7 to reflect this.

					with a Psychiatrist'.	
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	1	NICE	General	General	Lundbeck and Otsuka welcome the opportunity to provide a joint response to NICE in respect of this consultation on the draft guideline. Both Lundbeck and Otsuka have a rich heritage in improving the lives of those suffering with diseases of the central nervous system and have a long-standing alliance working in the area of psychiatry and neuroscience are currently working in partnership in the area of psychiatry and neuroscience. We warmly welcome the increased policy focus on areas of mental health, and firmly support the efforts towards parity of esteem for mental health. NICE's programme of work to develop quality standards and guidelines to support professionals is important and timely.	Thank you for your comments.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	2	Full	4.4.1	89	The role of carers across mental health conditions is critical and complex. As well as including carers' perspectives and involving them actively as part of the care team they also need support themselves. We strongly welcome the prominent inclusion in this draft guideline of recognition of the role of carers and emphasis on the importance of providing support and information. In addition to supporting individual patients and carers we believe that implementation of these particular recommendations will help to achieve the commitment set out clearly in *"Closing the Gap"* that carers will be better supported and more closely involved in decisions about mental health service provision.	Thank you for your comment, we agree with importance of including carers.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	3	Full	6.2.4	117	It is noted in 6.2.4 that Cipriani et al (1) found robust evidence. It should be noted that Fountoulakis and Siamouli (2), Glue and Tarr (3), Dervaux and Laqueille (4) and Grunze and Fyans (5) identified limitations with this analysis. The two primary limitations with the meta-analysis were using the three week discontinuation rate as a measure of treatment acceptability and failure to consider clinical differences between study populations (5). We note that there is a substantial variation in the	Thank you for your comment. Usually the treatment of mania is relatively short-term so the adverse longer term effects of anti-mania drugs are only relevant if these drugs are continued after the mania episode. However, later in the guideline, guidance is given on monitoring that is required with the longer term use of antipsychotic drugs. Cipriani et al set criteria for inclusion of studies in the meta-analysis and all studies that met these criteria

					results of Cipriani et al versus the new study results (Table 10) for aripiprazole (Mean change of YMRS -0.37 for Cipriani et al versus -0.63 for KANBA2012). Many tolerability issues will not emerge in the first three weeks of treatment, resulting in a bias in favour of medications with adverse events that emerge later on such as metabolic and endocrine disturbance (5). Due to a lack of information on the percentage of patients with rapid cycling, psychosis, mania and mixed states it is not clear what impact populations known to be refractory to treatment e.g. manic subpopulations have had in potentially biasing the meta-analysis results (5). *References* *1.Cipriani A, Barbui C, Salanti G, Rendell J, Brown R, Stockton S, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. The Lancet. 2011;378:1306-15.* *2.Fountoulakis KN, Siamouli M. Correspondence on Comparative efficacy of anti-manic drugs in acute mania. The Lancet. 2012;893-894.* *3.Glue P, Tarr G. Correspondence on Comparative efficacy of anti-manic drugs in acute mania. The Lancet. 2012;892.* *4.Dervaux A, Laqueille X. Correspondence on Comparative efficacy of anti-manic drugs in acute mania. The Lancet. 2012;893* *5.Grunze H, Fyans P. Correspondence on Comparative efficacy of anti-manic drugs in acute mania. The Lancet. 2012;893.*	were included. It is not possible to determine from the information in these studies whether there were any substantial differences between studies in terms of patients with treatment refractory mania. Regarding the variation in results between KANBA2012 and Cipriani et al. Given there are six trials of aripiprazole versus placebo, it is unlikely that adding one trial with CI that ranges from -0.88 to -0.37 would material change the results, thus the opinion of the GDG was that the 'inclusion of new studies would not change the conclusions of that review'.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	4	Full	6.2.5	125	In table 11 the cost of aripiprazole 15mg is incorrectly reported as £6.86 per day and £144.06 per three weeks. This is in fact the cost of the 30mg preparation. The actual cost of aripiprazole 15mg once a day is £3.43, and cost for three weeks is £72.03 (BNF, May 2014). The results of the decision analytic model should be updated in light of the incorrect unit costs for aripiprazole.	Thank you for spotting this – it has been amended. The results of the economic analysis have not been affected following correction of aripiprazole's acquisition cost: aripiprazole is still dominated by other treatment options (including haloperidol, risperidone, olanzapine, and quetiapine) and is therefore not cost-effective.
Lundbeck UK	5	Full	6.2.5	127	As a result, in table 12 the cost per person of	Thank you - this has been amended. The

Otsuka Pharmaceuticals UK (joint submission)					aripiprazole is also incorrectly reported to be £148.43. The correct cost is £76.40 (£72.03 + £4.37 [liver function test]).	results of the economic analysis have not been affected following correction of aripiprazole's acquisition cost: aripiprazole is still dominated by other treatment options (including haloperidol, risperidone, olanzapine, and quetiapine) and is therefore not cost-effective.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	6	Full	6.2.5	128 129	CG38 Bipolar Disorder recognised that: *"Individual variation in response to medication will often determine the choice of drug, as will the side effects and potential harms associated with each drug"*. We are therefore concerned by the limitations imposed upon the selection of treatments recommended for use by the economic analysis undertaken for this guideline. We agree with the limitations identified in this section regarding the economic analysis undertaken. Section 6.2.5 states: "*The economic analysis is very simplistic and has taken into account only costs associated with drug acquisition and additional laboratory tests required for each drug over a period of 3 weeks. This short time horizon was imposed by the short time horizons of the RCTs that were included in the meta-analysis that provided the effectiveness data. Side effects and their impact on costs and HRQoL were not considered in the analysis, due to the short time horizon and the lack of relevant data".* The section concludes: *"The results of the cost-utility analysis should be therefore interpreted with caution. In conclusion, the analysis has not overcome many of the limitations characterising previous studies. Factors such as acceptability, rate and type of side effects associated with each drug should also be considered when making recommendations."* We respectfully suggest that these limitations, combined with the emphasis on parity of esteem for people with mental health conditions, should not permit the proposed limitation of treatment options based on exclusion of such key considerations for both good treatment outcomes and patient experience.	The selection of treatments recommended for use in mania was not exclusively based on the economic analysis. It was made following consideration of the relative benefits, harms *and* the cost effectiveness of a range of drugs. In order to establish relative benefits and harms of drugs used in mania, the GDG considered the results of the network meta-analysis by Cipriani et al. This study ranked drugs by their overall probability to be best treatment according to their combined efficacy *and* acceptability, as reflected in drop-out rates. According to this analysis, the 4 overall best treatments in terms of combined efficacy and acceptability were haloperidol, olanzapine, risperidone and quetiapine. In addition to their higher clinical net health benefits, these drugs have also lower total acquisition & laboratory testing costs; hence they appear to be more cost-effective compared with other treatment options, regardless of any limitations of the economic modelling. Regarding the main limitation of the economic analysis, i.e. the use of a 3-week time horizon, as we explain in the full guideline report this was imposed by the 3-week time horizons of the RCTs that were included in the meta-analysis that provided the effectiveness data. Unfortunately, no longer-term data for all drugs assessed in the model were identified in the literature. Therefore, use of a longer time horizon would require use of assumptions on the long-term differential effects of the drugs

						included in the economic analysis and this was not deemed appropriate. Following the review of available clinical and economic evidence, a range of drugs are offered for the treatment of mania.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	7	Full	6.5.3	169	There are a number of limitations with the economic modelling which severely restrict the recommendations that can be made based upon the results. 1. The model time horizon was only three weeks long, failing to account for length of hospital stay beyond three weeks and resource use beyond three weeks. Eight weeks would be a more appropriate timeframe as it is the minimum period for recovery from acute mania (5). 2. The cost of aripiprazole used in the model was incorrect 3. Adverse events were not accounted for in the model. One of the most limiting factors of the modelling and subsequently the guidance is the failure to account for adverse events experienced on antipsychotic and mood stabiliser medications which affects adherence to medication and withdrawal. The adverse events can be severe and impact on the quality of life of patients. A recent Cochrane review found aripiprazole to be less likely than haloperidol to cause movement disorders such as parkinsonism and akathisia (6). In light of the limitations identified we believe the guidance should not utilise the economic modelling in making recommendations. Further to our concerns regarding section 6.2.5 above we also suggest that the statement that *"medications that are most clinically effective and reduce manic symptoms are expected to be also most cost effective"* does not suggest adequate recognition in development of the recommendations of treatments in this draft guideline of the impact of side effects or patient experience. With particular regard to aripiprazole we feel it is inappropriate to exclude an approved	Thank you for your comment. We are aware of the limitations of the economic model, and we acknowledge them in the guideline. Regarding your points: 1. As we state in the guideline, the time horizon of 3 weeks was imposed by the short time horizons (3 weeks) of the RCTs that were included in the meta-analysis that provided the effectiveness data. Unfortunately, we could not identify recovery data at 8 weeks for all drugs assessed in the model that would allow us to use a more appropriate time horizon in the economic analysis. Therefore, use of a longer time horizon would require use of assumptions on the long-term differential effects of the drugs included in the economic analysis and this was not deemed appropriate. 2. Thank you for pointing this out. This has now been corrected and aripiprazole has still the highest acquisition cost among the drugs assessed. 3. This has been acknowledged in the guideline. However, please note that the recommendations for mania were not exclusively based on the economic model. They were made following consideration of the relative benefits, harms and the cost effectiveness of a range of drugs. The network meta-analysis by Cipriani et al. on drugs for mania, which was considered by the GDG when making recommendations, ranked drugs by their overall probability to be best treatment according to their combined efficacy and

					treatment in standard use without more robust cost-effectiveness analysis. As recognised in TA292, albeit focussing on treatment of adolescents "*The Committee discussed the drug treatments available for adolescents and understood antipsychotics such as olanzapine, risperidone and quetiapine are routinely used off-label. Clinical specialists explained that it is important for adolescents with acute manic episodes to have a range of treatment options available. This is in order to individualise treatment…"* TA292 goes on to note that adolescents are often less tolerant of adverse reactions than adults, but the need for a range of treatments remains in adults, it being recommended that patients with bipolar disorder switch treatment when there is a lack of efficacy and/or intolerable adverse events that significantly impact on health or quality of life, or result in non-adherence to treatment (7). *References* *5.Grunze H, Fyans P. Correspondence on Comparative efficacy of anti-manic drugs in acute mania. The Lancet. 2012;893.* *6.Brown R, Taylor MJ, Geddes J. Aripiprazole alone or in combination for acute mania (Review). Cochrane Database of Systematic Reviews 2013.* *7.Young AH. Treatment of bipolar disorder with antipsychotic medication: issues shared with schizophrenia. J Clin Psychiatry; 68 (Suppl 6): 24–25, 2007*	acceptability, as reflected in drop-out rates (so, adherence to medication has been considered by the GDG). According to this analysis, the 4 overall best treatments in terms of combined efficacy and acceptability were haloperidol, olanzapine, risperidone and quetiapine. In addition to their clinical net health benefits, these drugs have also lower total acquisition & laboratory testing costs; hence they appear to be more cost-effective compared with other treatment options, regardless of any limitations of the economic modelling. The guideline does recommend a range of treatments for adults with mania, based on the available clinical and economic evidence.

Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	8	NICE/Full	1.5.3/ 6.6.1.3	172	We strongly welcome the recognition of the importance of patient preference in selecting an appropriate medication, and suggest that reference to inclusion of carers' views where appropriate is added to this section. We note that this has been done in CG178 where it states in section 1.3.5.1 "The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees".	Thank you for your comment. A recommendation has been added to the start of section 1.10 (revised recommendation number 1.10.1), which states that choice of any medication for psychotropic medication should consider the views of carers, if the service user consents.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	9	NICE/Full	1.5.3/ 6.6.1.3	172	We are concerned that there is no mention in this section of consideration and discussion of side effects relating to individual treatment options. Later in the draft guideline (7.6.1.11) it is stated that a healthcare professional should "Discuss and record the side effects that the person is most willing to tolerate" but neither there, nor in this section, is there confirmation of the importance of discussing the side effects of individual medications. Results from the Care Quality Commission's Community Mental Health Survey 2013 show that there has been little progress in increasing the proportion of patients who report that they are told about possible side effects of medication with 28% in 2011, 2012 and 2013 reporting that they were not told (8). The impact of side effects on individual patients' quality of life and their adherence to treatment can be significant and it is recommended that patients with bipolar switch treatment when there is a lack of efficacy and/or intolerable adverse events that significantly impact on health or quality of life, or result in non-adherence to treatment (7). References 7.Young AH. Treatment of bipolar disorder with antipsychotic medication: issues shared with schizophrenia. J Clin Psychiatry; 68 (Suppl 6): 24–25, 2007 8.Care Quality Commission. Community mental health survey 2013. http://www.cqc.org.uk/public/publications/surveys/com	Thank you for your comment. We agree that consideration of side effects is an important issue and we have added their consideration to recommendations 1.5.3 and 1.5.4.

					munity-mental-health-survey-2013	
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	10	NICE/Full	1.5.3/ 6.6.1.3	172	As stated above, we respectfully suggest that limitations in the economic analysis, combined with the emphasis on parity of esteem for people with mental health conditions should, not permit the proposed limitation of treatment options based on exclusion of such key considerations for both good treatment outcomes and patient experience.	Thank you for your comment. The selection of treatments recommended for use in mania was not exclusively based on the economic analysis. It was made following consideration of the relative benefits, harms and the cost effectiveness of a range of drugs. In order to establish relative benefits and harms of drugs used in mania, the GDG considered the results of the network meta-analysis by Cipriani et al. This study ranked drugs by their overall probability to be best treatment according to their combined efficacy and acceptability, as reflected in drop-out rates. According to this analysis, the 4 overall best treatments in terms of combined efficacy and acceptability were haloperidol, olanzapine, risperidone and quetiapine. In addition to their clinical net health benefits, these drugs have also lower total acquisition & laboratory testing costs, hence they appear to be more cost-effective compared with other treatment options. The guideline does recommend a range of treatments for adults with mania, based on the available clinical and economic evidence.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	11	NICE/Full	1.9.3/ 7.6.1.40	240	With reference to our point above to section 4.4.1 we suggest that the views of carers are also considered, where appropriate, in the decision to return a patient to primary care for further management.	Thank you for your comment. The guideline development group has added that a person should share a copy of the plan for transfer to primary care with their carers in recommendation 1.9.4.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	12	NICE/Full	1.2.4/ 7.6.1.44	240	We suggest that consideration is given to stressing the importance of engaging not just with people with bipolar disorder in primary care but also with their carers. We suggest that inspiration can be taken from the “Patient-centred care” section of CG38 Bipolar Disorder where there is a presumption in favour of carers being actively involved in discussions and decisions and an emphasis placed on clear communication.	Thank you for your comment, with which the guideline development group agrees. An addition has been made to recommendation 1.2.4 to engage with and develop a relationship with carers as well as service users.

Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	13	Full	1.2.4/ 7.6.1.44	240	We are concerned at the lack of progress in ensuring that patients being prescribed a medication for a mental health problem have their medication reviewed at least annually (as evidenced in the Care Quality Commission's *Community Mental Health Survey 2013*). Nearly one quarter of patients responding to the relevant question report that their medication has not been reviewed in the preceding 12 months, and there has been no change in this finding from 2012 (8). Knowing this to be the case, and accepting the importance of regular review, we suggest consideration is given to specifying a shorter timeframe for periodic review in order for the written language of "at least" every 12 months to be meaningful. *References* *8.Care Quality Commission. Community mental health survey 2013. http://www.cqc.org.uk/public/publications/surveys/community-mental-health-survey-2013*	Thank you for your comment. The GDG considered your argument and agreed that many cases should be reviewed more frequently than annually. However, it did not think that this should be applied in every case. Therefore the recommendation has been amended to indicate more frequent review should be carried out if there are any concerns from the person with bipolar disorder, their carers or health professionals, with at least annual review in anyone under long-term medication where there are no such concerns.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	14	Full	1.2.9/ 7.6.1.47	241	CG178 *"Psychosis and schizophrenia in adults: treatment and management"*, referenced elsewhere in the draft guidance as a provider of example text, notes that side effects should be included as grounds for re-referral to secondary care. We suggest that this should also be included in this guideline. For this to occur side effects must of course also be routinely monitored in primary care and such a requirement is not currently included. We find this surprising considering the importance of side effects in the management of bipolar stressed by group 1 in the scoping workshop for this guideline and also during the consultation on the scope of this guidance, not only by Lundbeck but also by Lancashire Care NHS Foundation and Rethink. Response to relevant comments in the scope consultation stated: *"Thank you for your comments, this guideline will be looking at side effects of medication (see section 4.3.1 k) and specifically interventions for weight gain (see section 4.3.2 b)."*	Thank you for your comment. The GDG agreed with your suggestion and recommendation 1.2.9 has been amended so that intolerable or medically important side effects would be a reason for referral to secondary care from primary care.

Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	15	NICE/Full	1.2.10-14/ 9.4.1.1 (to 9.4.1.5)	270	In CG38 Bipolar Disorder, which this draft guideline will replace, it is stated in section 1.6.3.1 that "If a person gains weight during treatment their medication should be reviewed". The requirement to review medication being used to manage bipolar disorder has been removed, and we suggest that such consideration should be restored.	Thank you for your comment. Since CG38, NICE has developed a range of relevant guidance on obesity that includes a consideration of medication as one of a number of causes of weight gain. Recommendations 1.2.11, 1.2.12 and 1.2.13 cover this and consideration of side effects is also referred to specifically in recommendation 1.5.4 in relation to medication.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	16	NICE/Full	1.2.12/ 9.4.1.3	271	CG178 *"Psychosis and schizophrenia in adults: treatment and management"* includes in its consideration of physical health the particular relevance in this population of determining smoking status and providing support for smoking cessation (at section 1.1.3.3). We suggest that such consideration is also included in this guideline with similar alert to the impact smoking can have on the metabolism of other drugs.	Thank you. Smoking cessation was outside of the scope of this guideline. However, in revised recommendation number 1.10.2 we do warn about smoking and its influence on drug metabolism.
Lundbeck UK Otsuka Pharmaceuticals UK (joint submission)	17	NICE/Full	1.11.10/ 10.8.1.3	296	As is recognised on page 273, line 34 "*At the time of publication, in the UK only one drug – Aripiprazole, which has been subject to a NICE Technology Appraisal (NICE, 2013a) -- is licensed for 12 weeks' treatment of moderate to severe manic episodes in bipolar I disorder in young people aged 13 years and older*." We respectfully submit that while this is the case it would be more appropriate to recommend aripiprazole first in the text of this section, then proceed if still considered appropriate to suggest that off label use of treatments recommended in adults may also be considered. As currently drafted the presumption appears to favour unlicensed options without robust comparisons of cost-effectiveness and safety having been conducted. We would note that guidance from the General Medical Council states that *"Prescribing unlicensed medicines may be necessary where…There is no suitably licensed medicine that will meet the patient's need"* (9). *References* *9.General Medical Council. Good practice in*	Thank you for your comment. This has been amended in line with your suggestion.

					prescribing and managing medicines and devices (2013). http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp	
Mersey Care NHS Trust	1	NICE/Full	1.5.2/ 6.6.1.2	171	In hypomanic episode in some instances clinicians might continue with antidepressants and add antipsychotic. However in manic episode antidepressants are stopped always	Thank you for your comment. The recommendation has been revised to say 'consider stopping the antidepressant' to take account of people with hypomania.
Mersey Care NHS Trust	2	NICE/Full	1.5.3/ 6.6.1.3	172	Consider Aripiprazole in manic episode as its licensed for this	Thank you for your suggestion. NICE guidelines recommend interventions that are most clinically and cost effective, based on best available evidence. Aripiprazole is licensed for manic episodes but it appears to be less effective and cost-effective than other drugs: The Cipriani et al. network meta-analysis, which was the main source of clinical evidence on drugs for mania that was utilised in this guideline, showed that aripiprazole ranked 6th among 14 treatment options (including placebo) in terms of combined efficacy and acceptability. Aripiprazole had also the highest acquisition cost among the drugs considered and was therefore overall less clinically and cost-effective than the drugs that are recommended in this guideline.
Mersey Care NHS Trust	3	Full	1.5.5/ 6.6.1.5	172	Alternative to Lithium would be Valproate if not responding to antipsychotic	Thank you for your comment, this is what the recommendation suggests.
Mersey Care NHS Trust	4	Full	1.5.6/ 6.6.1.6	172	Alternate to Lithium would be Valproate if not responding to antipsychotic	Thank you for your comment, this is what the recommendation suggests.
Mersey Care NHS Trust	5	Full	1.6.4/ 6.6.1.15	173	Anecdotally increase in Lithium doesn't always treat the depressive episode	Thank you for your comment. The GDG recognises that increase in lithium might not work for some people which is why the recommendation suggests alternatives. However the GDG did find evidence that increasing the dose of lithium to the higher part of the therapeutic range did reduce depressive symptoms.
Mersey Care NHS Trust	6	Full	1.6.5/ 6.6.1.16	174	Anecdotally increase in Valproate doesn't always treat depressive episode	Thank you for your comment. The GDG recognises that increase in valproate might not

						work for some people which is why the recommendation suggests alternatives.
Mersey Care NHS Trust	7	NICE/Full	1.10.24/ 7.6.1.30	239	Should blood monitoring for Valproate include clotting profile?	Thank you for your comment, a footnote regarding clotting is included in revised recommendation number 1.10.29.
Mersey Care NHS Trust	8	Full	1.6.8/ 6.6.1.19	21	This item needs clarity – discussion can be done at the point of resolution rather than wait for a further 4 weeks.	Thank you for your comment, with which the Guideline Development Group agrees. The recommendation has been changed to say '*Within* 4 weeks....' rather than '*At* 4 weeks...'
Mersey Care NHS Trust	9	NICE/Full	1.7.1/ 7.6.1.1	5 (to 31)	Is it necessary to provide "written information" after each episode; should this be a stand alone paragraph?	Thank you for your comment. The GDG judged that ideally written information should be provided in order to allow the person to make a fully informed decision about ongoing care. The provision of information is linked to the preceding discussion therefore the original structure has been retained.
Mersey Care NHS Trust	10	NICE/Full	1.7.5-1.7.6/ 7.6.1.2-7.6.1.3	33 (to 38)	Consider combining these two points and make clearer.	Thank you for your comment, but the guideline development group felt that these two recommendations needed to be separate because they relate to two different populations – those already on a drug and those potentially not on a drug.
Mersey Care NHS Trust	11	NICE/Full	1.10.8/ 7.6.1.14	4 (to 6)	"professional" would be better worded "provider	Thank you for your comment, but 'provider' is not usual NICE style for recommendations.
NHS Choices (Digital Assessment Service)	1	General	General	General	We welcome the guidance and have no comments as part of the consultation	Thank you.
NHS England	1	General	General	General	No comments.	Thank you.
Expert Reviewer 2	1	General (both)	General	General	The guideline should include a statement about offering all patients a second opinion (in line with other NICE guidelines) and offering non-responsive patients referral to tertiary level services (Tier 4 for CAMHS) with specialist expertise in the treatment of refractory bipolar disorder. There is evidence supporting this approach (eg: Kessing et al. 2013 B J Psych).	Thank you for your comment, this guideline is to be read alongside the service user experience in adult mental health guideline (NICE CG 136), which includes access to a second opinion. Tertiary level services were outside the scope of this guideline.
Expert Reviewer 2	2	NICE	1.1.6	16	While the management of comorbidities was outwith the scope of the GDG, simple reference to other NICE guidelines with regards to the management of, for example, anxiety in the context of bipolar disorder	Thank you for your comment. The GDG found very little specific evidence for or against specific treatments for anxiety disorders in bipolar disorder. In such circumstances it is

					appears weak and potentially misleading and harmful. First line pharmacological options for the management of GAD include SSRIs. Given the data show lack of efficacy of SSRIs in bipolar disorder and the concern that antidepressants may destabilise the disorder, this is a concern. At the very least there needs to be a caveat added to section 1.1.6	usual for NICE to recommendation consideration of existing NICE guidelines for the management of comorbid conditions.
Expert Reviewer 2	3	NICE	1.2.5	20	The evidence base for CBT either to treat bipolar depression or prevent its recurrence is not as strong as is suggested, eg: in the prevention of bipolar recurrence the largest RCT to date by Scott J et al (Br J Psych. 2006; 188:313-20) showed no effect of CBT versus treatment as usual. In addition caveats are needed before extrapolating from the much stronger and supportive evidence base for using CBT in unipolar depression to bipolar depression. There is increasing evidence that the two forms of depression are distinct in their clinical features and responsivity to medication and psychological treatments.	Thank you for raising this issue. The GDG discussed this again, but decided not to change 'offer' to 'consider' in recommendations 1.2.5 and 1.6.1. In doing so, they took into account the totality of evidence and came to the consensus that at present there is insufficient evidence to conclude that the two forms of depression are distinct. Therefore, they thought that a stronger recommendation was warranted. Please also note that we have amended recommendation 1.6.1 (NICE guideline) to make it clear that the healthcare professional should discuss with the person with bipolar disorder the possible benefits and risks of psychological interventions and monitor mood carefully for signs of mania or hypomania or deterioration of the depression symptoms. In addition, recommendation 1.6.2 makes it clear that psychological therapists working with people with bipolar depression should have training in, and experience of, working with people with bipolar disorder.
Expert Reviewer 2	4	NICE	1.2.5	20	Many primary care services (eg IAPTS) routinely exclude all bipolar patients (bipolar I and II) with the result that patients with mild or moderate BP depression cannot access treatment in primary care but will often not meet the threshold for access secondary services. As a result such bipolar patients are often untreated. This is a major clinical problem. Some comment from NICE about the appropriateness of minor/moderate depressive episodes in BP 1 and 2 disorder (without major risk) being managed in primary	Thank you for your comment. We agree that people with bipolar disorder should not be excluded from psychological treatment and a likely provider of such treatment would be IAPT. Hence, the recommendation that people with bipolar depression should receive psychological treatment is a key recommendation. However, NICE does not usually name a specific provider of such services. It has specified that such treatment

					care services would be helpful to patients.	should be delivered by health professionals with experience of bipolar disorder and also that the severity of depression must be considered.
Expert Reviewer 2	5	NICE	1.2.12	21	Please add thyroid function checks here.	Thank you for your comment, monitoring thyroid function has been added to the recommendation.
Expert Reviewer 2	6	NICE	1.3.5	23	There is a lack of evidence to support the contention that bipolar disorder should be managed in EIP services for the first 3 years and no evidence that the outcome for BPD in UK EI teams is superior to the outcome for such patients treated in CMHTs.	Thank you. People entering EIS services are people with either a 'prodromal syndrome' or people with early psychosis. Many of those people with early psychosis will end up with a diagnosis of bipolar disorder. For all people in EIS the outcomes are better than for people in standard care (a CMHT). It would be odd to treat only those with bipolar who present with a psychosis and suggest that all other people (when they present with hypomania but not mania) they should be referred elsewhere. The GDG does however concede that there is some variation in service provision, and has therefore revised the recommendation to set out the components of the teams that should provide assessment for bipolar disorder, rather than stating that the team must be EIS. Please note, recommendation 1.3.5 has been merged with revised recommendation 1.3.1.
Expert Reviewer 2	7	NICE	1.5.3		*NICE guideline: section 1.5.3, page 25* *Full guideline: sections 6.2 & 6.5* While one accepts that there is good data for the haloperidol in mania, one would question it being placed at number 1 in this list (albeit it being probably an alphabetical list). The rate of EPS will be high if higher doses are used as it will be in difficult cases. The main reason for its demotion would be the lack of continuation/long term treatment data. It is a good principle which I urge NICE to adopt that one should treat mania with an agent that one can continue into the longer term. It is not clear why aripiprazole has not been included as an option for acute mania. There is only a	Thank you for your comment. You are right, we are required to use alphabetical order unless there is very good evidence for a ranking. It should be noted that if we did use rank from network meta-analysis, this would give false impression that haloperidol was clinically better as it would still come out as number 1. We agree that side effects need to be considered too. Aripiprazole was not included as an option based on clinical and economic evidence. Section 6.2 has been amended to include a description of the ranking of drugs by their

					statement in section 6.2.5 that it has a high acquisition cost. Aripiprazole will shortly be available as a generic which should reduce its acquisition cost. Aripirpazole is licensed to treat acute mania and also licensed for subsequent maintenance treatment with a particular effect on reducing the frequency of manic relapses. It has a relatively favourable tolerability profile. One would throw doubt about the high place for risperidone in this Guideline. This analysis includes the Khanna et al. 2005 B J Psych study conducted in India. This showed a drug-placebo difference in the order of 12-13 YMRS points after 3 weeks. This is way more than all the other large RCTs of antipsychotics in acute mania. For comparison another risperidone RCT showed just over a 5 point difference (Hirschfiled et al. Am J Psych 2004) – very in keeping with other antipsychotics. The difference in the Indian study was that baseline YMRS scores were over 37. Baselines in most large industry conducted mania studies are in the order of 29-30 demonstrating that the Indian patients were markedly more severely ill. The completion rate in the Indian study was over 95% which again is much higher than most large industry studies in acute mania (usually around the 65-70% mark). This will help accentuate the drug-placebo difference. Clearly the population was rather different in the Indian study and this in part explains the large effect size seen. Furthermore, the mean dose of risperidone was 5.6 mg which is close to the upper limit of recommended doses in the SPC. The mean weight of the patients was 56 kg much lower than found in western mania samples. It is not therefore surprising that the EPS rate on risperidone was 35%. Such rates are unacceptably high in a population of patients that one wishes in most cases to go onto continuation/long term treatment. Another reason to "demote" risperidone is that its continuation/long term treatment data is weak. Adding this one study with such a large effect size into the multiple treatment meta-analysis has distorted the data	overall probability to be best treatment according to their combined efficacy and acceptability, as reported in Cipriani et al. network meta-analysis. According to this analysis, aripiprazole ranked 6th among 14 treatment options (including placebo). Moreover, it has the highest acquisition cost compared with the other drugs for acute mania that were assessed in the economic analysis. The guideline economic analysis showed that aripiprazole was not cost-effective as it was dominated by other treatment options. We do acknowledge the fact that aripiprazole will soon become available as generic, and we have now highlighted the need for re-assessment of cost effectiveness of drugs when these become generic [section 6.2.5, in *discussion – limitations of the economic analysis*]. The need for re-assessment of the cost effectiveness of aripiprazole for the treatment of mania once it has become generic has been noted by the Surveillance team at NICE. Regarding the issue about inclusion of Khanna 2005, this study has been included in the network meta-analysis because it met the pre-defined inclusion criteria, according to the review protocol (see corresponding Appendix in Cipriani et al., 2011 – Lancet). It should be noted that although the mean drug-placebo difference is greater in Khanna than the other studies, so is the variance. Therefore, the SMD is within the confidence intervals of most other study SMDs. Nevertheless, in order to address your comment about over-reliance on data from this network meta-analysis, we carried out two sensitivity analyses excluding Khanna 2005 (both for efficacy and acceptability) and we

					with regards to risperidone in comparison with other drugs not tested in similar populations. For the reasons given above my view is that the Khanna study is not representative or generalizable and should be withdrawn from the meta-analysis. My recommendation for 1.5.3 is that you should say quetiapine or olanzapine as favoured options but that aripiprazole, haloperidol or risperidone are also options in some circumstances.	found that results were materially no different: Efficacy (continuous data) Original analysis including Khanna2005: SMD -0.59 (95% CI -0.76, -0.42)' I^2 = 44% Sensitivity analysis excluding Khanna2005: SMD -0.51 (95% CI -0.66, -0.37); I^2 = 0% Acceptability (drop-out rate, dichotomous outcome): Original analysis including Khanna2005: RR 0.50 (95% CI 0.38, 0.66); I^2 = 1% Sensitivity analysis excluding Khanna2005: RR 0.57 (95% CI 0.42, 0.78); I^2 = 0% This information will be added to the full guideline report. The GDG discussed the other issues you raised, but came to the conclusion that they had to base their decisions on the currently available costs and evidence.
Expert Reviewer 2	8	NICE	1.5.5	25	Many factors need to be considered in this clinical scenario and it is often far more acceptable to a patient and the clinical team to add valproate to an antipsychotic especially in a male patient. One of the issues is speed of response. Lithium has the drawback that the dose can only be increased about every 10 days (7 days to get steady state and then inevitably several days waiting for the lithium level to come back from the lab). Even when appropriate levels of lithium are achieved as quickly as possible the clinical response is still slower than with valproate and this may be unacceptable in some circumstances. There is good data that valproate in combination often gains control of mania in a shorter time period than lithium in combination. It is recommended that either is given as an option depending on the clinical scenario.	Thank you for your comment. The GDG considered lithium as the preferred choice of drug as it has a better profile than valproate in the long term management of bipolar disorder. However, as with all NICE guidelines, this has to be used with clinical judgement and if there were clinical circumstances in which valproate might be preferable to lithium then the prescriber would select valproate over lithium in that situation.
Expert Reviewer 2	9	NICE	1.6.3	27	It is surprising that some much weight has been given to the use of olanzapine plus fluoxetine in the	Thank you for raising these issues. With regard to the combination of fluoxetine and

					management of bipolar depression when this is based on relatively weak studies with low numbers of patients treated with the combination and no fluoxetine only arm (e.g. Tohen et al. Arch Gen Psych 2003 – combination n= 82, placebo n = 355 and olanzapine only n = 351). It is even more surprising that any recommendation is made about olanzapine monotherapy for bipolar depression. Reviewing the evidence suggests that, even if there is a significant difference in MADRS score between olanzapine and placebo, this is driven entirely by non- specific effects of olanzapine. For example in the Tohen et al. 2003 study, compared to placebo, olanzapine monotherapy significantly reduced "inner tension" and increased sleep and appetite. However there was no significant effect on apparent or reported sadness or pessimistic thoughts (all of which improved on olanzapine plus fluoxetine). The data is most clear for quetiapine in the management of bipolar depression and this should be acknowledged with this drug being the first to be mentioned. There may be a difference in Asian populations with olanzapine monotherapy possibly being more clearly effective (Tohen M B J Psych 2012), which is not mentioned anywhere – which is strange given that it is explicitly stated that differences between ethnic groups would be considered.	olanzapine, we used a network meta-analysis, which allows both direct and indirect evidence to be included in one model. However, the GDG did take into account your concern about the low numbers of participants in the combination studies, but on balance believe that the recommendation should stand. With regard to quetiapine, as described in section 6.5.2 of the full guideline "GDG determined that service users may have different preferences based on prior experience, and they may value side effects differently. For these reasons, the GDG decided to recommend that service users and clinicians choose among several pharmacological interventions with favourable ratios of benefits to harms." With regard to a differential treatment effect in Asian populations, although this is an important issue, there is insufficient evidence to draw conclusions at this stage (we note that Tohen do not make this claim).
Expert Reviewer 2	10	NICE	1.6.3 (to 1.6.7)	27 28	Many audits have demonstrated that many patients with bipolar disorder in the UK are prescribed antidepressants. Some guidance needs to be provided regarding this. At the very least there should be a statement that antidepressants should not be used alone in the absence of an antimanic treatment. "If a person develops moderate or severe bipolar depression and is already taking valproate, consider increasing the dose " There is no evidence for positive dose response for valproate in bipolar depression and so this recommendation should be withdrawn.	Thank you for your comments. The GDG has carried out a systematic search of studies of the effects of antidepressants on mania and switching into mania and hypomania, and found inconsistent evidence of a possible very small adverse effect of antidepressants on switching. As a result the GDG decided to make only a consider stopping the antidepressant recommendation if a person was taking antidepressants and developed mania or hypomania. The GDG was not able to make any recommendation on the long-term use of antidepressants in view of this

						inconsistent evidence. Revised recommendation number 1.6.5 has been amended to reflect that the dose of valproate should only be increased so that the blood level is within the therapeutic range. The GDG agrees there is no evidence for the effectiveness of valproate doses above the therapeutic range.
Expert Reviewer 2	11	NICE	1.7.5 1.7.6	31	Valproate continues to have a prominent place in long term treatment options. There is only one placebo controlled maintenance study of valproate (Bowden et al. 2000) which was entirely negative. The Balance study showed it to be less effective than lithium, however there was no placebo so we do not know what valproate alone' s efficacy is from this study. It is also surprising that ariprprazole and asenapine have not been included as long term options for patients who have responded to them acutely (as per the recommendation for quetiapine).	Thank you for your comment. We were unable to carry out a meta-analysis as the trials were not conducted in a similar enough way. Therefore a narrative synthesis of RCTs was done. The GDG placed greater weight on the considerations of the Balance trial due to the care with which it was undertaken, and the power and clinical significance of the trial. Other comparable trials tended to be discontinuation trials. In section 6.2 of the full guideline we have added a description of the ranking of drugs by their overall probability to be best treatment according to their combined efficacy and acceptability, as reported in Cipriani et al. network meta-analysis. According to this analysis, aripiprazole ranked 6th and asenapine ranked 10th among 14 treatment options (including placebo). Moreover, aripiprazole and asenapine have higher acquisition costs compared with the other drugs for acute mania that were assessed in the economic analysis. Both drugs were shown not to be cost-effective in the guideline economic analysis as they were dominated by other treatment options. We do acknowledge that aripiprazole will soon be available as generic, and we have highlighted the need for re-assessment of cost

						effectiveness of drugs when these become generic [section 6.2.5, in *discussion – limitations of the economic analysis*].The need for re-assessment of the cost effectiveness of aripiprazole for the treatment of mania once it has become generic has been noted by the Surveillance team at NICE.
Expert Reviewer 2	12	NICE	1.10.3 1.10.6	35 36	Hypotension and hypertension with most widely used antipsychotics are rare side effects as long as the medications are prescribed appropriately and in line with SPC. There does not seem to be a good rationale for doing this routinely before starting treatment- although it is indicated if there are specific indications (e.g. clozapine is used, the patient has a history of cardiac disease or has presented with postural hypotension previously). Obtaining accurate measurements in acutely unwell patients is likely to be challenging and the recommendation to check after every dose change problematic and not evidenced based.	Thank you for your comments. The GDG found evidence that there was occasionally substantial and even life threatening harm due to cardiovascular events even in people with unsuspected cardiovascular disease. Therefore whenever possible the cardiovascular checks recommended in the guidelines should be performed as recommended in the guideline.
Expert Reviewer 2	13	NICE	1.10.16	38	"Measure the person's serum lithium level every 6 months " This is inconsistent with the FULL guidelines, which state (p238, line 15) "According to the GDG expert opinion, laboratory tests that are required specifically for people receiving long-term therapy with lithium include: • Over 1 year: **four** tests of serum lithium concentration, two tests of renal function (urea, creatinine and electrolytes); two tests of thyroid function; and two tests of calcium levels. " It is strongly recommended that you remain consistent with the full guideline.	Thank you for your comment. The guideline development group has considered your and others' comments and have revised the recommendation to say that everyone taking lithium should have their levels checked every 3 months for the first year (see revised recommendation number 1.10.18)..
Expert Reviewer 2	14	NICE	1.10.26	39	It states that valproate should be stopped immediately if abnormal LFTs are detected. Mild elevation of LFTs is common with valproate, as it is with many anticonvulsant drugs and it is often transient or non-progressive – it is not a reason to stop valproate. Please define what is meant by abnormal LFTs and/or add that clinical judgement is needed as to whether to	Thank you. This is helpful. A footnote has been added to the recommendation that reads: *Although the absolute values of hepatic enzymes are a poor indicator of the extent of hepatic damage, it is generally accepted that if these are persistently elevated to over 3 times*

					stop valproate or continue it with closer monitoring of the LFTs.	*the upper normal limit, continuing to rise or accompanied by clinical symptoms, the suspected drug should be withdrawn. Raised hepatic enzymes of any magnitude accompanied by reduced albumin or impaired clotting suggest severe liver disease.*
Expert Reviewer 2	15	NICE	1.11.10	42	It is not clear why it is recommended not continue antipsychotic treatment beyond 12 weeks when treating a young person for mania. It may take longer than 12 weeks to achieve stability, particularly if the first antipsychotic used is ineffective. This does not take into consideration the severity of the illness, treatment non-response, relapse prevention and significant risks associated with the illness. In such cases, the benefits of longer-term medication often outweigh the risks. It is also discriminatory as the adult guidance doesn't limit the time allowed to treat, and these limits were not in the guidance for psychosis in young people. In many cases when an antipsychotic has been effective one would want to continue it as a maintenance treatment especially if there is good evidence for such use (quetiapine, olanzapine and aripiprazole are all licensed as maintenance agents in BPD and although not licensed there is good evidence that risperidone is effective in preventing manic relapse in patients who had a manic episode that responded to risperidone). The draft acknowledges that there may be some YP who may benefit from longer term treatment ('most' not 'all' is used in line 21, page 294 Full Guideline), but then goes on to categorically state that long-term treatment should not be used. In light of all the comments above, it would be helpful if this statement could be re-considered. One way round the problem is to recommend that all young people on an antipsychotic for 12 weeks have a multidisciplinary review, one issue for which could be continuation of medication.	Thank you for your comment. The recommendation on aripiprazole comes from the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be "routinely" continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
Expert Reviewer 2	16	NICE	1.11.12 (to	42 43	This recommendation that medication shouldn't be considered for BP depression until 3 months of	Thank you for your comment. The Guideline Development Group believes the wording in

			1.11.15)		psychotherapy has been tried may cause real problems on the ground. Such therapy may well not be available given the skill needed to deliver it to this population or not available at the time needed. This recommendation also does not take into consideration the severity of the illness, treatment non-response and significant risks associated with the illness. In view of both these issues ,this recommendation needs to be tempered.	recommendations 1.11.12 and 13 was misleading therefore it has been clarified. The intention was not to suggest that medication should not be considered until after 3 months of psychological therapy. The group thinks the confusion may have arisen because it states 4 to 6 *sessions* rather than 4 to 6 *weeks*. This has been rectified. The Guideline Development Group agrees that risk needs to be considered and have therefore added a recommendation to take this into account.
Expert Reviewer 2	17	NICE	1.11.7	41	The guidelines state 'Do not diagnose Bipolar II disorder in children and young people'. There is concern re diagnosis of hypomania in youth. However if both caution and adult criteria are used surely the diagnosis while rare could be made? This recommendation seems to be based on a Consensus conference held nearly 9 years ago. There must be some data that bears on this point in the intervening period. If not, then either another consensus must be undertaken or the recommendation softened to say something like "It is not recommended…."	Thank you for your comment. This recommendation has been removed and the 'evidence to recommendations' section in the full guideline has been amended.
Expert Reviewer 2	18	NICE	1.7.2 (to 1.7.4)	30 31	There are a number of negative psychological intervention studies in Bipolar disorder (eg Scott, Frank, Meyer) which give indications of those patients who do not seem to benefit. Data from patients with mixed features also reveals poor response to psychological interventions. The recommendation should be tempered to reflect the fact that not all patients are suitable for this. The wide variation of 9-25 sessions reflects the fact that evidence from a lot of different therapies has been conflated (and that the evidence is probably too weak for each therapy modality individually). One would doubt whether data from disparate pharmacological studies would be allowed to be combined in this way! Does group psychoeducation work in 9 sessions? There is no evidence for this but yet the net effect of	Thank you for your comment. Evidence was provided that unlike pharmacological interventions, the many different forms of psychological treatment that have been shown to be effective do in fact share a set of specific approaches that vary little in nature from one approach to another. Therefore individual psychological treatments were grouped together, group psychological treatments were grouped together and family treatments were grouped together. If there was evidence of heterogeneity was identified then the GDG considered the sources of heterogeneity. The GDG agrees that although the broad treatment approaches share many features in common and in their effectiveness, they vary in the way

					this strong recommendation is that 9 sessions of this could be given. This recommendation should be modified to take these issues into account.	that they should be conducted, including the number of sessions. Therefore the number of sessions for each treatment has not been specified and the reader is referred to published manuals of the treatment approach for specific detail on how they should be conducted.
Expert Reviewer 2	19	Full	10.1	273 line 34	Further clarity on the status of lithium would be helpful – the SPC states that it is not recommended in under 12s, implying that it can be prescribed in those 12 and over.	Thank you for your comment. This is an unusually difficult area, depending upon the brand of lithium used. Priadel tablets, Priadel liquid, Li-Liquid and Camcolit tablets are only licensed for 18 years upward. The only preparation that does have a license from age 12 upwards is Liskonum tablets. The BNFc lists Camcolit as well as Liskonum as options in 12 years and above despite only one of them being licensed. It is not clear why Camcolit is listed as an option for children, but the manufacturer of Camcolit has previously confirmed that it is definitely *not* licensed in this age group. The manufacturer was unsure why the BNF has not indicated the fact that it is not licensed as there is usually a statement to that effect when they include drugs without licenses. The statement has therefore been modified to say that *some* preparations of lithium are licensed for use in those over 12 years.
Expert Reviewer 2	20	Full	10.1	274 line 36 (to 38)	The statement on fish oils could be more circumspect – it implies effectiveness in a range of disorders.	Thank you for your comment, we agree and the statement has been modified, omitting reference to wider use.
Expert Reviewer 2	21	Full	1.11.15/ 10.8.1.8	296	This recommendation takes no consideration of levels of severity and ability to engage with psychological treatment; in severe high risk cases of depression often young people struggle to engage in psychological treatment and may need a pharmacological intervention much sooner than after several months of attempted psychological treatment. Even modest improvement with a pharmacological intervention may aid engagement in the psychological treatment.	Thank you for your comment. The Guideline Development Group believes the wording in recommendations 1.11.12 and 13 was misleading therefore it has been clarified. The intention was not to suggest that medication should not be considered until after 3 months of psychological therapy. The group thinks the confusion may have arisen because it states 4 to 6 *sessions* rather than 4 to 6 *weeks*. This

					Further there is no evidence currently demonstrating the efficacy of CBT in managing bipolar depression	has been rectified. The Guideline Development Group agrees that risk needs to be considered and have therefore added a recommendation to take this into account.
Rethink Mental Illness	1	NICE	General	General	Rethink Mental Illness welcomes the updated guideline and the inclusion of more holistic elements such as physical health care and employment support. This matches the tone set in the updated 'Psychosis and schizophrenia in adults' guidelines (CG178). We also welcome the emphasis on involving people with bipolar disorder and their carers/families in decisions about care and treatment, including advance statements and crisis planning.	Thank you for your comments.
Rethink Mental Illness	2	NICE	1.1.12 (to 1.1.19)	17 18	We are pleased to see this strengthened section on support for carers and in particular the section on information-sharing. This is an area that can be misunderstood by health professionals and can result in families and carers being inappropriately excluded from discussions on grounds of confidentiality. Rethink Mental Illness produced a briefing on this issue (available at http://www.carersandconfidentiality.org.uk/wp-content/uploads/2008/12/1110_54-briefing-paper.pdf) and also has a factsheet on confidentiality and information sharing for families and carers, available at http://www.rethink.org/resources/c/confidentiality-and-information-sharing-for-carers-friends-and-family-factsheet.	Thank you for your comments.
Rethink Mental Illness	3	NICE	1.2.11	21	This section has been adapted from CG178. In CG178 the point at which responsibility for physical health monitoring transfers from secondary to primary care is set at 12 months or when the person's conditions has stabilised, whichever is longer. In the proposed updated bipolar disorder guidelines, the timeframe is just when a person's condition has stabilised. If evidence suggests the 12 month timeframe would be applicable for bipolar disorder, we would recommend its specific inclusion in this section. Often people's	Thank you for your comment, this has now been clarified in revised recommendation number 1.10.9, using the wording from CG178.

					physical healthcare falls through the gap between primary and secondary care so it would be helpful to have this clarified as far as possible, as in CG178.	
Rethink Mental Illness	4	NICE	1.8.4 1.8.5	32	We welcome this section on ensuring that providers are auditing and monitoring the physical health support they offer.	Thank you for your comment.
Royal College of Nursing	1	Full	General	General	The structure of the guidance is now outdated and is not user friendly. Our members felt that it was too medically orientated with not enough focus on recovery.	Thank you for your comment. The Guideline Development Group agrees that a focus on recovery is important, and endeavoured in its guideline to capture this as far as the evidence would allow. Recovery is given some prominence in the recommendations about carers (1.1.14, 1.1.18) and primary care (1.2.4), and the section on 'Promoting recovery and return to primary care' sets out the service context. In response to your comment, the GDG has**,** in addition, strengthened recommendation 1.1.1 in the guideline to emphasis recovery and building relationships, and added the importance of personal recovery goals to revised recommendation 1.3.2.
Royal College of Nursing	2	Full	1.9.3	33	How long a patient is required to have been stable before they are offered the option to move back to primary care needs to be defined. E.g. why not mention the use of the outcome measures CROM 4 factor model and the MHCT that is nationally mandated since 2010	Thank you for your comment, such policies are not usually referred to in NICE guidelines as they may become outdated before the guideline is reviewed and redrafted.
Royal College of Nursing	3	Full	General	General	There is poor content from the social, employment, accommodation, relationships contexts especially when considering relapse contingency planning	Thank you for your comment, this guideline is to be read alongside the service user experience in adult mental health guideline (NICE CG 136), which includes a number of recommendations regarding the social aspects you have listed.
Royal College of Nursing	4	Full	General	General	There is no reference made to the forensic aspects or to learning disabilities	Thank you for your comment, care for people with mental health problems in forensic settings will be covered in the forthcoming NICE guideline on mental health in prisons. Specific interventions for people with learning disabilities are not covered as part of the

						scope of this guideline, although recommendation 1.1.5 does state that people with learning disabilities and bipolar disorder should be offered the same services. It is likely that the treatment of people with learning disabilities and bipolar disorder will be covered by two guidelines that are currently in development: 'Challenging behaviour and learning disabilities' and 'Mental health and learning disabilities'.
Royal College of Paediatrics and Child Health	1	General	General	General	No comments.	Thank you.
Royal College of Psychiatrists	1	NICE	General	General	Revision of the 2006 NICE Bipolar Guideline is timely. The evidence base has increased markedly since the previous guideline particularly for pharmacotherapy. The new guideline is commendable in places but there are many points in this draft that need to be reconsidered as listed below and in present form it is unacceptable.	Thank you for your comments, we will address your concerns where they appear.
Royal College of Psychiatrists	2	General (both)	General	General	Bipolar disorder is a common and complex clinical condition and outcomes are frequently poor. The updated guidelines should include a statement about making available to all patients an expert second opinion (in line with other NICE guidelines) and offering non-responsive patients referral to tertiary level services with specialist expertise in the treatment of refractory bipolar disorder. There is some evidence supporting the benefits of this approach (e.g.: Kessing et al. 2013 B J Psych).	Thank you for your comment, this guideline is to be read alongside the service user experience in adult mental health guideline (NICE CG 136, recommendation 1.3.4), which includes access to a second opinion. Tertiary level services were outside the scope of this guideline.
Royal College of Psychiatrists	3	NICE	General	General	Bipolar disorder is one of the most comorbid psychiatric disorders with reported rates of psychiatric comorbidity of 75% and high rates of comorbid physical ill-health also reported. Some further comments on the importance and management of comorbidity, particularly alcohol and substance abuse, would be helpful.	Thank you for your comments. The section at the start of the guideline – "Treatment and support for specific populations" – refers professionals to the guidelines for conditions which are commonly comorbid with Bipolar Disorder. These include borderline and antisocial personality disorders, generalised anxiety disorder, substance misuse problems, problems experienced around birth for the mother, people with a learning disability and

						the aging population. We recognise that there is little evidence for the treatment of comorbidities, but our experience of doing guidelines addressing treatment when there are two or more conditions suggests we should treat both conditions as you would if the person had one condition. Following this guideline alongside another for the comorbidity seems to be the right treatment strategy.
Royal College of Psychiatrists	4	NICE	1.6.1	12	For consistency you should add the caveat to psychological interventions: "Discuss with the person the possible benefits and risks for this intervention"	Thank you for your comment, with which the Guideline Development Group agrees. The sentence you have suggested has been added to the recommendation.
Royal College of Psychiatrists	5	NICE	1.1.6	16	While the management of co-morbidities was out with the scope of the GDG, simple reference to other NICE guidelines with regards to the management of, for example, anxiety in the context of bipolar disorder appears weak and potentially misleading. First line pharmacological options for the management of GAD include SSRIs. Given the extant data show lack of efficacy of SSRIs in bipolar disorder and the concern that antidepressants may worsen the course of the disorder, this is a concern. At the very least there needs to be a caveat added to section 1.1.6	Thank you for your comment. The GDG found very little specific evidence for or against specific treatments for anxiety disorders in bipolar disorder. In such circumstances it is usual for NICE to recommendation consideration of existing NICE guidelines for the management of comorbid conditions.
Royal College of Psychiatrists	6	NICE	1.2.5	20	The evidence base for CBT either to treat bipolar depression or prevent its recurrence is not as strong as is suggested, e.g.: in the prevention of bipolar recurrence the largest RCT to date by Scott J et al (Br J Psych. 2006; 188:313-20) showed **no** effect of CBT versus treatment as usual. A strength of the Scott et al paper was the representative nature of the patient sample. The guidance should accurately reflect these data. Major depressive disorder and bipolar disorder are distinct diagnostic categories. The justification for extrapolating from the much stronger and supportive evidence base for using CBT in unipolar depression to bipolar depression is highly questionable and is not evidence based. There is increasing evidence that the two forms of depression are distinct not least with	Thank you for raising this issue. The GDG discussed this again, but decided not to change 'offer' to 'consider' in recommendations 1.2.5 and 1.6.1. In doing so, they took into account the totality of evidence and came to the consensus that at present there is insufficient evidence to conclude that the two forms of depression are distinct. Therefore, they thought that a stronger recommendation was warranted. Please also note that we have amended recommendation 1.6.1 (NICE guideline) to make it clear that the healthcare professional should discuss with the person with bipolar disorder the possible benefits and risks of psychological interventions and monitor mood

					regards to treatment.	carefully for signs of mania or hypomania or deterioration of the depression symptoms. In addition, recommendation 1.6.2 makes it clear that psychological therapists working with people with bipolar depression should have training in, and experience of, working with people with bipolar disorder.
Royal College of Psychiatrists	7	NICE	1.2.5	20	Many primary care services (eg IAPTS) routinely exclude all bipolar patients (bipolar 1 and 2) with the result that patients with mild or moderate BP depression cannot access treatment in primary care but often may not meet the threshold to access secondary services. As a result such bipolar patients are often untreated. This is a major clinical problem. Some comment from NICE about the appropriateness of minor/moderate depressive episodes in BP 1 and 2 disorder (without major risk) being managed in primary care and how this should be best accomplished would be helpful to patients.	Thank you for your comment. We agree that people with bipolar disorder should not be excluded from psychological treatment and a likely provider of such treatment would be IAPT. Hence, the recommendation that people with bipolar depression should receive psychological treatment is a key recommendation. However, NICE does not usually name a specific provider of such services. It has specified that such treatment should be delivered by health professionals with experience of bipolar disorder and also that the severity of depression must be considered.
Royal College of Psychiatrists	8	NICE	1.2.12	21	Please add thyroid function for lithium	Thank you for your comment, monitoring thyroid function has been added to the recommendation.
Royal College of Psychiatrists	9	NICE	1.3.5	23	There is little evidence to support the suggestion that bipolar disorder should be managed in EIP services for the first 3 years. Furthermore, we question the ability of many EIP services to do this except in the case of a patient presenting with mania or a psychotic episode for the following reasons: first, and most important, it is not clear that most EI services have the knowledge or skills to do this as their training is geared to assessing and managing prodromal schizophrenia and early psychoses, if EI teams are to take on BPD then it will require a major investment in retraining; secondly, many patients with bipolar disorder don't have psychotic symptoms when acutely ill and most EI services have 'psychosis' as an entry criteria, finally, there is an absence of evidence that the outcome for bipolar disorder in UK EI teams is superior to the	Thank you for your comment. EIS, as you say, deal with prodromal and actual psychosis. These two categories will include people later diagnosed with bipolar disorder. If a person has only been depressed but not psychotic, they will be treated in IAPT of in a CMHT. If they then develop a psychosis or hypomania, they are best placed in a team that can deal with this – an EIS team. The outcome for people with psychosis in EIS is well established. The trials include people who later are found to have bipolar and schizophrenia. The outcomes for both are better than for standard care. The GDG does however concede that there is some variation in service provision, and has

					outcome for such patients treated in CMHTs.	therefore revised the recommendation to set out the components of the teams that should provide assessment for bipolar disorder, rather than stating that the team must be EIS. Please note, recommendation 1.3.5 has been merged with revised recommendation 1.3.1.
Royal College of Psychiatrists	10	Full	6.2 & 6.5		*NICE version: section 1.5.3, page 25* *Full version: sections 6.2 & 6.5* It is not clear why asenapine and aripiprazole have not been included as options for acute mania. In section 6.5 for the full guideline there is a statement that the "GDG decided not to recommend interventions that have not been shown to be clinically efficacious for the treatment of acute mania (that is, asenapine…..)". However no evidence is presented in section 6.2 to justify this. Arirpirazole is not included in the list of non-efficacious treatments and again there is no evidence based justification in 6.2 or 6.5 as to why it is not included. There is only a statement in section 6.2.5 that it has a high acquisition cost. There is an argument to support including these two treatment options. As is stated in 6.5 "service users may have different preferences based on prior experience and they may value side effects differently". Two major references to asenapine in mania are omitted and are thus not even discussed e.g. asenapine (mean 18.2 mg/d) was rapidly effective, well tolerated and as effective as olanzapine (n = 488, RCT, d/b, p/c, 3/52, McIntyre *et al, Bipolar Disord* 2009; 11: 673–86), superior to placebo at day 2 and with less weight gain than olanzapine (n = 488, RCT, d/b, p/c, 3/52, McIntyre *et al, J Affect Disord* 2010; 122: 27–38). Aripirpazole is licensed to treat acute mania and also licensed for subsequent maintenance treatment. When the tolerability of antipsychotic drugs is considered, both drugs have a relatively favourable tolerability profile (Haddad PM, Sharma S. CNS Drugs 2007; 21(11):911-36). Finally, aripiprazole will shortly be available as a generic which should reduce its	Thank you for your comment. We have now amended the statement in section 6.5, as asenapine and ziprasidone have been indeed shown to be efficacious compared with placebo for the treatment of mania. In section 6.2 we have added a description of the ranking of drugs by their overall probability to be best treatment according to their combined efficacy and acceptability, as reported in Cipriani et al. network meta-analysis. According to this analysis, aripiprazole ranked 6th and asenapine ranked 10th among 14 treatment options (including placebo). Moreover, aripiprazole and asenapine have higher acquisition costs compared with the other drugs for acute mania that were assessed in the economic analysis. Both drugs were shown not to be cost-effective in the guideline economic analysis as they were dominated by other treatment options. We do acknowledge that aripiprazole will soon be available as generic, and we have highlighted the need for re-assessment of cost effectiveness of drugs when these become generic [section 6.2.5, in *discussion – limitations of the economic analysis*].The need for re-assessment of the cost effectiveness of aripiprazole for the treatment of mania once it has become generic has been noted by the Surveillance team at NICE. Regarding the two McIntyre papers, these had been included in the Cipriani et al network

					acquisition cost. There has been an over-reliance on the Cipriani et al. 2011 multiple treatment metanalysis in coming to conclusions about treatment of acute mania, without acknowledging the shortfalls of this analysis which are considerable. For example, this analysis includes the Khanna et al. 2005 B J Psych study of risperidone conducted in India. This showed a drug-placebo difference in the order of 12-13 YMRS points after 3 weeks. This is considerably more than all the other large RCTs of antipsychotics in acute mania. For comparison another risperidone RCT showed just over a 5 point difference (Hirschfiled et al. Am J Psych 2004) – very much in keeping with other antipsychotics. The difference in the Indian study was that baseline YMRS scores were over 37 and the body mass of the participants less. Baselines in most large industry conducted mania studies are in the order of 29-30 demonstrating that the Indian patients were markedly more severely ill. The completion rate in the Indian study was over 95% which again is much higher than most large industry studies in acute mania (usually around the 65-70% mark). This will help accentuate the drug-placebo difference. Clearly the population was rather different in the Indian study and this in part may explain the large effect size seen. Adding this one study with such a large effect size into the multiple treatment meta-analysis has distorted the data with regards to risperidone in comparison with other drugs not tested in a simpler population. We recommend that these caveats are at least acknowledged and that the Cipriani et al meta-analysis be considered carefully in light of its drawbacks.	meta-analysis published in the Lancet in 2011 (McIntyre 2009 is reference 23 on page 15 and the second one is reference 6 on page 18 of the Supplementary web appendix of the Lancet paper). The second one is reported with the "unpublished name" of A7501004 because it was included in the analyses before its journal publication. On page 19 and 20 of the same supplementary file you can check the study characteristics. Regarding the issue about inclusion of Khanna 2005, this study has been included in the network meta-analysis because it met the pre-defined inclusion criteria, according to the review protocol (see corresponding Appendix in Cipriani et al., 2011 – Lancet). It should be noted that although the mean drug-placebo difference is greater in Khanna than the other studies, so is the variance. Therefore, the SMD is within the confidence intervals of most other study SMDs. Nevertheless, in order to address your comment about over-reliance on data from this network meta-analysis, we carried out two sensitivity analyses excluding Khanna 2005 (both for efficacy and acceptability) and we found that results were materially no different: Efficacy (continuous data) Original analysis including Khanna2005: SMD -0.59 (95% CI -0.76, -0.42); I^2 = 44% Sensitivity analysis excluding Khanna2005: SMD -0.51 (95% CI -0.66, -0.37); I^2 = 0% Acceptability (drop-out rate, dichotomous outcome): Original analysis including Khanna2005: RR 0.50 (95% CI 0.38, 0.66); I^2 = 1%

						Sensitivity analysis excluding Khanna2005: RR 0.57 (95% CI 0.42, 0.78); I^2 = 0% This information will be added to the full guideline.
Royal College of Psychiatrists	11	NICE	1.5.5	25	We are not clear about the recommendation that lithium, in preference to valproate, is added to an antipsychotic in an episode of mania that has only partially responded to an antipsychotic. Many factors need to be considered in this clinical scenario and it is often far more acceptable to a patient and the clinical team to add valproate to an antipsychotic especially in a male patient. Lithium has the drawback that the dose can only be increased about every 10 days (7 days to get steady state and then inevitably several days waiting for the lithium level to be reported). Valproate thus may often allow control of mania in a shorter time period than lithium. The footnote that sodium valproate does not have marketing authorisation for some indications may confuse: perhaps the semisodium valproate part could be placed earlier so as not to possibly confuse people that valproate itself isn't licensed	Thank you for your comment. We agree that the evidence supporting the use of lithium and valproate as additional treatments to antipsychotics for acute mania is comparable. However, the GDG considered lithium as the preferred choice of drug as it has a better profile than valproate in the long term management of bipolar disorder. As with all NICE guidelines, this has to be used with clinical judgement and if there were clinical circumstances in which valproate might be preferable to lithium then the prescriber would select valproate over lithium in that situation.
Royal College of Psychiatrists	12	NICE	1.6.3	27	It is surprising that some much weight has been given to the use of olanzapine plus fluoxetine in the management of bipolar depression when this is based on relatively weak studies with low numbers of patients treated with the combination and no fluoxetine montherapy arm (e.g. Tohen et al. Arch Gen Psych 2003 – combination n= 82, placebo n = 355 and olanzapine only n = 351). It is even more surprising that any recommendation is made about olanzapine monotherapy for bipolar depression. Reviewing the evidence suggest that even if there is a significant difference in MADRS score between olanzapine and placebo, this is driven entirely by non-specific effects of olanzapine on sleep, appetite and tension. However there was no significant effect on apparent or reported sadness or pessimistic thoughts (all of which improved on olanzapine plus fluoxetine).	Thank you for raising these issues. With regard to the combination of fluoxetine and olanzapine, we used a network meta-analysis, which allows both direct and indirect evidence to be included in one model. However, the GDG did take into account your concern about the low numbers of participants in the combination studies, but on balance believe that the recommendation should stand. With regard to quetiapine, as described in section 6.5.2 of the full guideline "GDG determined that service users may have different preferences based on prior experience, and they may value side effects differently. For these reasons, the GDG decided to recommend that service users and clinicians choose among several pharmacological

					The data is most clear for quetiapine in the management of bipolar depression and we feel this should be acknowledged with this drug being the first to be mentioned and the strength of the supporting evidence fully discussed. There may be a difference in Asian populations with olanzapine monotherapy possibly being more clearly effective (Tohen M et al, B J Psych 2012), which is not mentioned anywhere – which is strange given that it is explicitly stated that differences between ethnic groups would be considered.	interventions with favourable ratios of benefits to harms." With regard to a differential treatment effect in Asian populations, although this is an important issue, there is insufficient evidence to draw conclusions at this stage (we note that Tohen do not make this claim).
Royal College of Psychiatrists	13	NICE	1.6.3 (to 1.6.7)	27 28	Many audits have demonstrated that many patients with bipolar disorder in the UK are prescribed antidepressants. Some guidance needs to be provided regarding this. At the very least there should be a statement that antidepressants should not be used alone in the absence of an antimanic treatment especially in patients with bipolar I. "If a person develops moderate or severe bipolar depression and is already taking valproate, consider increasing the dose " We were unaware of any evidence for positive dose response for valproate in bipolar depression.	Thank you for your comments. The GDG has carried out a systematic search of studies of the effects of antidepressants on mania and switching into mania and hypomania, and found inconsistent evidence of a possible very small adverse effect of antidepressants on switching. As a result the GDG decided to make only a consider stopping the antidepressant recommendation if a person was taking antidepressants and developed mania or hypomania. The GDG was not able to make any recommendation on the long-term use of antidepressants in view of this inconsistent evidence. Revised recommendation number 1.6.5 has been amended to reflect that the dose of valproate should only be increased so that the blood level is within the therapeutic range. The GDG agrees there is no evidence for the effectiveness of valproate doses above the therapeutic range.
Royal College of Psychiatrists	14	NICE	1.7.3	30	"Offer a structured, manualised psychological intervention (individual, group or family) designed for bipolar disorder to prevent relapse or for people who have some persisting symptoms between episodes of mania or bipolar depression." Such an intervention may be designed for bipolar disorder but no quality evidence is put forward for	Thank you for your comment. As described in section 8.2 of the full guideline, the GDG concluded that the evidence suggests that psychological interventions may improve symptoms and reduce the risk of relapse and hospitalisation for people with bipolar depression. This evidence is presented in

					efficacy and this seems to be an expression of faith rather than being based on evidence.	section 8.1 of the full guideline. However, the GDG acknowledged that the evidence for particular psychological interventions varies in quality. The GDG also noted that the evidence for psychological interventions for unipolar depression is consistent with the evidence for bipolar depression and of much higher quality.
Royal College of Psychiatrists	15	NICE	1.7.5	31	The directive to explain to patients "that lithium is the most effective long-term treatment for bipolar disorder" is not based on comparative evidence. Apart from the Balance study where it was superior to valproate (although the design of the study may have confounded this against valproate), we are not aware of any other long term study in bipolar disorder where lithium was shown to be superior to other long term treatment options. Similarly, longer term continuation studies of antipsychotics have apparently been discounted to some extent.	Thank you for your comment. As acknowledged in the full guideline (7.5) the evidence base is relatively poor and the GDG used their expert judgement when drafting this recommendation. Having considered this further, they stand by the recommendation.
Royal College of Psychiatrists	16	NICE	1.7.5	31	Surprisingly, valproate has a prominent place in long term treatment options. There is only one placebo controlled maintenance study of valproate (Bowden et al. 2000) which was negative. The Balance study showed it to be less effective than lithium, however there was no placebo so we do not know valproate's actual efficacy is from this study. It is also surprising that ariprprazole and asenapine have not been included as long term options for patients who have responded to them acutely (as per the recommendation for quetiapine).	Thank you for your comment. As acknowledged in the full guideline (7.5) the evidence base is relatively poor and the GDG used their expert judgement when drafting this recommendation. Having considered this further, they stand by the recommendation. In section 6.2 of the full guideline we have added a description of the ranking of drugs by their overall probability to be best treatment according to their combined efficacy and acceptability, as reported in Cipriani et al. network meta-analysis. According to this analysis, aripiprazole ranked 6th and asenapine ranked 10th among 14 treatment options (including placebo). Moreover, aripiprazole and asenapine have higher acquisition costs compared with the other drugs for acute mania that were assessed in the economic analysis. Both drugs were shown not to be cost-effective in the

						guideline economic analysis as they were dominated by other treatment options. We do acknowledge that aripiprazole will soon be available as generic, and we have highlighted the need for re-assessment of cost effectiveness of drugs when these become generic [section 6.2.5, in *discussion – limitations of the economic analysis*].The need for re-assessment of the cost effectiveness of aripiprazole for the treatment of mania once it has become generic has been noted by the Surveillance team at NICE.
Royal College of Psychiatrists	17	NICE	1.10.3-1.10.6	35 36	Hypotension and hypertension with most widely used antipsychotics are rare side effects as long as the medications are prescribed appropriately and in line with SPC (e.g., don't start immediately with a high dose of quetiapine) and significant side-effects will be picked up by history or routine blood pressure monitoring. Obtaining accurate measurements in acutely unwell patients is likely to be challenging. There does not seem to be a good rationale for adding this routinely before starting treatment- although it is indicated if there are specific indications (e.g., when clozapine is used, if the person has a history of cardiac disease or has presented with postural hypotension previously etc. – clearly in these case P & BP monitoring is important).	Thank you for your comments. The GDG found evidence that there was occasionally substantial and even life threatening harm due to cardiovascular events even in people with unsuspected cardiovascular disease. Therefore whenever possible the cardiovascular checks recommended in the guidelines should be performed as recommended in the guideline.
Royal College of Psychiatrists	18	NICE	1.10.16	38	"Measure the person's serum lithium level every 6 months " This is inconsistent with the FULL guidelines, which state (p238, line 15) "According to the GDG expert opinion, laboratory tests that are required specifically for people receiving long-term therapy with lithium include: - At initiation of treatment: 3 tests of serum lithium concentration in order to establish the drug's therapeutic dose - Over 1 year: **four** tests of serum lithium concentration, two tests of renal function (urea, creatinine and electrolytes); two tests of thyroid	Thank you for your comment. The guideline development group has considered your and others' comments and have revised the recommendation to say that everyone taking lithium should have their levels checked every 3 months for the first year (see revised recommendation number 1.10.18)..

					function; and two tests of calcium levels. “ We would strongly recommend consistency with the full guideline not least because if you recommend 6-monthly, practically that results in every 6-9 months or longer in the community. To say 3 months at least results in 3 tests in a year in most people.	
Royal College of Psychiatrists	19	NICE	1.10.26	39	It states that valproate should be stopped immediately if abnormal LFTs are detected. Mild elevation of LFTs is common with valproate, as it is with many anticonvulsant drugs, and is often transient or non-progressive – it is not a reason to stop valproate. Please define what is meant by abnormal LFTs or write that clinical judgement is needed as to whether to stop valproate or continue it with closer monitoring of the LFTs.	Thank you. This is helpful. A footnote has been added to the recommendation that reads: *Although the absolute values of hepatic enzymes are a poor indicator of the extent of hepatic damage, it is generally accepted that if these are persistently elevated to over 3 times the upper normal limit, continuing to rise or accompanied by clinical symptoms, the suspected drug should be withdrawn. Raised hepatic enzymes of any magnitude accompanied by reduced albumin or impaired clotting suggest severe liver disease.*
Royal College of Psychiatrists	20	NICE	1.11.10	42	It is not clear why it is recommended to not continue antipsychotic treatment beyond 12 weeks when treating a young person for mania. It may take longer than 12 weeks to achieve full stability, particularly if the first antipsychotic used is ineffective. In many cases when an antipsychotic has been effective one would want to continue it as a treatment especially if there is good evidence for such use (quetiapine, olanzapine and aripiprazole are all licensed as maintenance agents in bipolar disorder and although not licensed there is good evidence that risperidone is effective in preventing manic relapse in patients who had a manic episode that responded to risperidone)	Thank you for your comment. The recommendation on aripiprazole comes from the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be “routinely” continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
Royal College of Psychiatrists	23	Full	10.1	274 line 36 (to 38)	The statement on fish oils could be more circumspect – it implies effectiveness in a range of disorders.	Thank you for your comment, we agree and the statement has been modified, omitting reference to wider use.
Royal College of Psychiatrists	24	Full	10.7.2	293 line 19	Although it is important to minimise use of AAPs due to adverse effects, the statement that they can only be	Thank you for your comment. The recommendation on aripiprazole comes from

				(to 22)	used for 12 weeks is extremely concerning. This does not take into consideration the relatively rare but very serious, high risk cases of adolescent BP that are admitted to inpatient units, who are often difficult to treat. These YP often need trials of different AAPs in order to establish the best risk/benefit profile for each YP. They may also have chronic relapsing conditions, and each relapse may be associated with high risk suicide attempts and other risks such as vulnerability to sexual exploitation. In these cases the benefits of longer-term medication often outweighs the risks. Even within this draft , the expert opinion is quoted from the aripiprazole appraisal (pg 283) which states that the average duration of AAP treatment in YP can reach 12 months (and in rare cases possibly longer). Thus these recommendations ignore this expert opinion and also discriminate against young people with a serious disorder. In addition, this time limit is not stipulated in the psychosis guidelines, hence this draft is at odds with other expert opinion. Research also suggests that affective disorder is a leading cause of suicide in YP and that these cases are undertreated (Windfuhr JCPP 2008).	the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be "routinely" continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
Royal College of Psychiatrists	26	Full	10.7.4	295 line 11 (to 20)	Again, this draft is incongruent with the guidance on psychosis which states that there is a high risk of relapse if AAPs are stopped within 1-2 years of an episode. This sends a very confusing and contradictory message to clinicians and service users: if there is a BP episode with psychosis, then AAPs can be used for up to 2 yrs but only for 12 weeks without psychosis, although the risk of adverse effects is the same.	Thank you for your comment. The GDG recognised the growing evidence of harms associated with antipsychotics, especially those in most common use at the time of writing (olanzapine, quetiapine etc) which are strongly associated with metabolic syndromes such as diabetes. However, given the lack of evidence regarding the efficacy of <u>any</u> pharmacological treatment of bipolar disorder in children and young people, the GDG therefore decided to extrapolate from the adult data, which prioritises antipsychotics over lithium and valproate for acute mania. Because bipolar disorder is a relapsing and remitting condition that rarely becomes chronic, the use of antipsychotics is bound to be needed for shorter amounts of time than in people with

						schizophrenia where psychotic episodes are longer and become chronic. The only drug licenced is aripiprazole, which is the subject of a technology appraisal, and both the licence and the TA limit the use of aripiprazole to 12 weeks. However, we do take your point that sometimes antipsychotics are needed for longer than 12 weeks, and have therefore amended the recommendation to say that drug treatment should not 'routinely' continue for longer than 12 weeks, and that at 12 weeks there should be a multidisciplinary review to assess whether to continue treatment.
Royal College of Psychiatrists	27	NICE/Full	1.11.10/ 10.8.1.3	296	See above: Again, this draft is incongruent with the guidance on psychosis which states that there is a high risk of relapse if AAPs are stopped within 1-2 years of an episode. This sends a very confusing and contradictory message to clinicians and service users: if there is a BP episode with psychosis, then AAPs can be used for up to 2 yrs but only for 12 weeks without psychosis, although the risk of adverse effects is the same.	Thank you for your comment. There is very little evidence regarding the efficacy of any antipsychotic treatment of bipolar disorder in children and young people. However, there is growing evidence of the harms associated with the antipsychotics, especially those in most common use at the time of writing (olanzapine, quetiapine etc) which are strongly associated with metabolic syndromes such as diabetes. Because bipolar disorder is a relapsing and remitting condition that rarely becomes chronic, the use of antipsychotics is bound to be needed for shorter amounts of time than in people with schizophrenia where psychotic episodes are longer and become chronic. The only drug licenced is aripiprazole, which is the subject of a technology appraisal, and both the licence and the TA limit the use of aripiprazole to 12 weeks. However, we do take your point that sometimes antipsychotics are needed for longer than 12 weeks, and have therefore amended the recommendation by adding the word 'routinely'.
Royal College of Psychiatrists	30	Full	10.1	274 line 19 (to 23)	It should be noted that this guidance is out of date, is currently being reviewed and recent Cochrane meta-analyses provide a more up-to-date review of the evidence for treatment (eg Cox; Hetrick 2012)	We accept the view expressed, however, this is the guidance currently in practice. Reference is now made to the more up-to-date Cochrane review (Hetrick et al., 2012).

Royal College of Psychiatrists	31	NICE/Full	1.11.7/5.6.1.24	110	Would prefer wording such as care/caution to be exercised when diagnosing bipolar II in under 18s rather than carte blanche approach.	Thank you for your comment. This recommendation has been removed and the 'evidence to recommendations' section in the full guideline has been amended.
Expert Reviewer 3	1	Full	5 8		This is an impressively careful, fair-minded, thoughtful, and clear document. It seems as though it will be extremely helpful to researchers and practitioners.	Thank you for your comments.
Expert Reviewer 3	2	Full	5	91 (to 110)	More detail regarding the level of sensitivity and specificity for the child assessments would be helpful. For example, describing the level of success of Youngstrom's instruments could provide guidance for those trying to learn about assessment options. It is not clear why those studies were excluded given that he recruited from outpatient practice centers.	Thank you for your comment. The paper in question was excluded in our search because it did not diagnose anyone with bipolar disorder so there was no gold standard by which sensitivity, specificity, positive predictive value etc could be calculated. It therefore did not meet the inclusion/exclusion criteria for the search because of its methodological limitations.
Expert Reviewer 3	3	Full	5.2.2	94	It might be helpful to define that university samples were not included in the review.	Thank you for this suggestion, but we did not explicitly exclude university samples, and would have included if all other inclusion criteria were met.
Expert Reviewer 3	4	Full	5.4	102	I was pleased to see the strong statement on rapid cycling and the lack of consistent evidence regarding treatment.	Thank you for your comment.
Expert Reviewer 3	5	NICE/Full	1.3.2/ 5.6.1.5	107	I found the suggestion to screen for "episodes of disinhibition" less precise than I might hope for. This type of symptom might be frequently observed in personality disorders and other externalizing conditions as well. Perhaps drawing the cardinal symptoms from the diagnostic criteria would provide slightly more clarity in wording. This may be a distinction between US and UK diagnostic systems, but I was surprised not to see mention of mood changes.	Thank you for your comment, the recommendation has been amended to read: *overactivity and disinhibition or other episodic and sustained changes in behaviour.*
Expert Reviewer 3	6	Full	8.1	242	This statement is confusing: "There have been no studies evaluating psychological interventions for mania or hypomania." Some researchers have tested whether psychological interventions help prevent manic symptoms, and others have included those with manic symptoms at baseline.	Thank you for your comment. None of the interventions reviewed were specifically designed to address acute mania per se. It is true that there is some evidence on manic relapses and subsyndromal manic symptoms and therefore the guideline has been amended to read: "*There have been no studies evaluating psychological interventions for*

						acute mania or hypomania."
South London and Maudsley NHS Foundation Trust's CAMHS department.	1	Full	General	General	We should solidly welcome the guideline for bipolar disorder in young people as it provides a rational basis for clinical decision making. It is comprehensive work and the committee should be congratulated for the amount of effort they have invested. There are all sorts of important information and analyses in the guidelines as well as good clinical guidance. However, I was disappointed by some of the stipulations concerning treatment. I list my concerns below and I am happy to elaborate further on my concerns as needed. I know that several other researchers and clinicians in the field are worried about these recommendations.	Thank you for your comments, we will address your concerns where they appear.
South London and Maudsley NHS Foundation Trust's CAMHS department.	2	NICE/Full	1.11.10/ 10.8.1.3	294	Whilst it is very important not to prescribe any medication beyond the time period necessary, it would be damaging to stop antimanic medication prematurely. This would increase the risk for manic or depressive relapse with potentially detrimental effects on the young person's health. This stipulation goes against NICE's own guidance for antipsychotic medication to treat psychosis in young people, and NICE's own guidance for antipsychotic medication in adult bipolar. Moreover, it is unprecedented—no guidelines that I am aware of have such a restrictive and potentially dangerous stipulation. I can foresee that clincians will very sensibly flout this stipulation in order to serve the best interests of their patients. I cannot imagine how a clinician—knowing about the high probabilitly of relapse upon premature withdrawal—would follow these guidance and withhold treatment from a young person. Following this stipulation could severely undermine the trust of the patient and their family to the clinician and the organization they work for.	Thank you for your comment. The recommendation on aripiprazole comes from the NICE technology appraisal on the use of this drug, which reflects that aripiprazole has a UK marketing authorisation for up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in young people aged 13 and older. The GDG has however taken your comments into account, and those from several other stakeholders, and revised recommendations 1.11.9 and 1.11.15 to state that antipsychotic treatment should not be "routinely" continued for longer than 12 weeks, and that at 12 weeks a full multidisciplinary review should be undertaken to assess whether treatment should continue.
South London and Maudsley NHS Foundation Trust's CAMHS department.	3	NICE/Full	1.11.12-14/10.8.1.5-.7	296	Bipolar depression is a potentially lethal condition for which there is no evidence in young people that it improves with CBT. There is also little evidence that bipolar depression is effectively treated with CBT or IPT. By contrast, anitpsychotic treatment—either using quetiapine or combined olanzapine with fluoxetine or,	Thank you for your comment. The GDG did find evidence that psychological treatments were effective in bipolar depression. The GDG found no trial evidence to support the use of antipsychotic drugs in bipolar depression but as a second line treatment or more urgently

					recently, lurasidone—are efficacious in adults and are the mainstay of treatment. There is some evidence that these drugs may work in children (particularly olanzapine combined with fluoxetine), though further well-conducted trials are needed. It would seem cruel to withhold potentially effective treatments from young people with bipolar depression, a condition causing terrible distress and impairment. Such a stipulation would have similar effects to the 12-week stipulation: damage patients and seriously undermine the patient-doctor relationship.	after multidisciplinary review agree that on the basis of extrapolation from evidence in adults that drug treatments recommended for bipolar depression in adults could also be used in children and young people.
South London and Maudsley NHS Foundation Trust's CAMHS department.	4	NICE	1.11.7	41	The authors of the guidelines are very right to be concerned about over-diagnosing or over-treating bipolar disorder in children. However, the solution to these problems should be rigorous diagnosis and treatment monitoring, rather than arbitrary restrictions to practice. The guidance makes several sensible recommendations about how to improve diagnosis and the need for specialist assessments. I wholeheartedly support these. In terms of treatment monitoring: the authors of the guidelines are primarily concerned about the metabolic side effects of antipsychotic medication and rightly so. However, these are side effects that are relatively easy to monitor and potentially to modify. I would suggest that the focus should be on improving the monitoring of side effects as well as information on how to minimize the potential for side effects (diet, exercise etc).	Thank you for your comment. This recommendation has been removed and the 'evidence to recommendations' section in the full guideline has been amended.

These organisations were approached but did not respond:

2gether NHS Foundation Trust
5 boroughs NHS Foundation Trust Partnership
AbbVie
Ability West
ABPI Pharmaceutical Serious Mental Illness Initiative
Action on Postpartum Psychosis
Adults Strategy and Commissioning Unit

Adverse Psychiatric Reactions Information Link
Afiya Trust
Africa Advocacy Foundation
Alder Hey Children's NHS Foundation Trust
All Wales Senior Nurses Advisory Group
Allocate Software PLC
Anxiety Alliance
Anxiety Care UK
Anxiety UK
Archimedes Pharma Ltd
ASSIST Trauma Care
Assocation of NHS Occupational Physicians
Association for Dance Movement Psychotherapy UK
Association for Family Therapy and Systemic Practice in the UK
Association for Psychoanalytic Psychotherapy in the NHS
Association for Rational Emotive Behaviour Therapy
Association of Anaesthetists of Great Britain and Ireland
Association of Child Psychotherapists, the
Association of Dance Movement Therapy UK
Association of Therapeutic Communities
Astrazeneca UK Ltd
Autism West Midlands
Bengali Women's Group forum
Betsi Cadwaladr University Health Board
Big White Wall
Birmingham City Council
Black Health Agency
Black Mental Health UK
Black People's Mental Health Association
Boots
BPDWORLD
Bristol Myers Squibb Pharmaceuticals Ltd
British Acupuncture Council
British Association for Behavioural & Cognitive Psychotherapies
British Association for Counselling and Psychotherapy
British Association for Music Therapy
British Association of Art Therapists
British Association of Dramatherapists
British Association of Psychodrama and Sociodrama
British Association of Social Workers

British Geriatrics Society
British Medical Association
British Medical Journal
British Muslim Forum
British National Formulary
British Nuclear Cardiology Society
British Pharmacological Society
British Psychoanalytic Council
British Psychological Society
British Red Cross
Buckinghamshire County Council
C. R. Bard, Inc.
Calderdale and Huddersfield NHS Trust
Calderstones Partnerships NHS Foundation Trust
Cambridgeshire & Peterborough Mental Health Trust
Camden Carers Centre
Camden Link
Campaign Against Living Miserably CALM
Capsulation PPS
Capsulation PPS
Care Quality Commission
Carers Trust
Central & North West London NHS Foundation Trust
Central London Community Health Care NHS Trust
Centre for Mental Health
Centro de Terapia Familiar
Chartered Physiotherapists in Mental Health
Chinese Mental Health Association
Chinese National Healthy Living Centre
CIS' ters
Citizens Commission on Human Rights
Clarity Informatics Ltd
Clifford Beers Foundation
College of Mental Health Pharmacists
Combat Stress
Community Links
Contact
Crisis
Critical Psychiatry Network
Croydon Clinical Commissioning Group

Croydon Health Services NHS Trust
Croydon University Hospital
Cumberland Infirmary
Cumbria Partnership NHS Trust
Cyberonics
Cygnet Health Care
Cygnet Hospital Harrow
David Lewis Centre, The
Department for Education
Department of Health, Social Services and Public Safety Northern Ireland
Depression Alliance
Depression UK
Derbyshire County Council
Devon Partnership NHS Trust
Division of Education and Child Psychology
Doctors Support Network
Dorset Mental Health Forum
Drinksense
Dudley and Walsall Mental Health Trust
East and North Hertfordshire NHS Trust
East Sussex County Council
Eastbourne District General Hospital
Eating Disorder Association (NI)
Eli Lilly and Company
Empowerment Matters
Equalities National Council
Essex County Council
Ethical Medicines Industry Group
Expert Patients Programme CIC
Faculty of Forensic and Legal Medicine
Faculty of Public Health
Fighting Strokes
First Person Plural
FirstSIGNS aka LifeSigns
Five Boroughs Partnership NHS Trust
Foundation for People with Learning Disabilities
Fremantle Hospital
George Eliot Hospital NHS Trust
GfK Bridgehead
GlaxoSmithKline

Glencare
Gloucestershire LINk
Gorlin Syndrome Group
GP update / Red Whale
Great Western Hospitals NHS Foundation Trust
Greater Manchester & Beyond Coalition of PLW & HIV
Greater Manchester West Mental Health NHS Foundation Trust
Hafal Wales
Hafan Cymru
Hampshire Partnership NHS Trust
Handicapped Families Council
Harrow Local Involvement Network
Health & Social Care Information Centre
Health and Care Professions Council
Healthcare Improvement Scotland
Healthcare Infection Society
Healthcare Inspectorate Wales
Healthcare Quality Improvement Partnership
Healthwatch East Sussex
Hearing Voices Network
Hertfordshire Partnership NHS Foundation Trust
Hertfordshire Partnership NHS Trust
Herts Valleys Clinical Commissioning Group
Hindu Council UK
Hiraeth Services Ltd
Hockley Medical Practice
Holistic stress management
HQT Diagnostics
Human Givens Institute
Humber NHS Foundation Trust
Independent Children's Homes Association
Independent Healthcare Advisory Services
Information Centre for Health and Social Care
Integrity Care Services Ltd.
IRIS
Janssen
Kent and Medway NHS and Social Care Partnership Trust
Lancashire LINk
Leeds and York Partnership Foundation Trust
Leeds Community Healthcare NHS Trust

Leeds South and East Clinical Commissioning Group
Leeds Teaching Hospitals NHS Trust and Leeds Radiology Academy
Lesbian & Gay Foundation
Lilly UK
Local Government Association
London Metropolitan Police
London Respiratory Team
Lonsdale Medical Centre
Luton and Dunstable Hospital NHS Trust
Making Space
Maternal Mental Health Alliance
Medicines and Healthcare products Regulatory Agency
Mellow Campaign
Mencap
Mental Health Act Commission
Mental Health Alliance
Mental Health and Substance Use: dual diagnosis
Mental Health Foundation
Mental Health Group British Dietetic Association
Mental Health Matters
Mental Health Nurses Association
Mental Health Providers Forum
Middlesex University
Mild Professional Home Ltd
Mind
Mind Wise New Vision
Mind Wise New Vision
Mindfulness Centre of Excellence
Ministry of Defence (MOD)
Monash Health
Muslim Council of Britain
Muslim Health Network
National Association for Gifted Children
National Association for People Abused in Childhood
National Association of Primary Care
National Autistic Society
National Clinical Guideline Centre
National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health
National Collaborating Centre for Women's and Children's Health

National Deaf Children's Society
National Institute for Health Research Health Technology Assessment Programme
National Institute for Health Research
National Institute for Mental Health in England
National Nurse Consultants in CAMHS forum
National Patient Safety Agency
National Public Health Service for Wales
National Self Harm Network
National Society for the Prevention of Cruelty to Children
National Voices
Network of Sikh Organisations UK
Neurolink
NHS Barnsley Clinical Commissioning Group
NHS Confederation
NHS Connecting for Health
NHS County Durham and Darlington
NHS Cumbria Clinical Commissioning Group
NHS Greater Manchester Commissioning Support Unit
NHS Hardwick CCG
NHS Health at Work
NHS Herefordshire
NHS Improvement
NHS Leeds West CCG
NHS Luton CCG
NHS Milton Keynes
NHS North Somerset CCG
NHS Plus
NHS South Cheshire CCG
NHS Wakefield CCG
NHS Warwickshire North CCG
Niger Delta University
North East Essex Clinical Comissioning Group
North Essex Mental Health Partnership Trust
North of England Commissioning Support
North Staffordshire Combined Healthcare NHS Trust
North West London Hospitals NHS Trust
Northumberland, Tyne & Wear NHS Trust
Nottingham Healthcare NHS Trust
Nottinghamshire Acute Trust
Nottinghamshire Healthcare NHS Trust

Nursing and Midwifery Council
OCD Action
Outlook Care
Oxford Health NHS Foundation Trust
Oxfordshire Clinical Commissioning Group
Oxleas NHS Foundation Trust
P.T.S.D.
PAPYRUS
Parenteral and Enteral Nutrition Group
Parkwood Healthcare
Patient Assembly
PERIGON Healthcare Ltd
Pharmaceutical Mental Health Initiative
Pharmametrics GmbH
PHE Alcohol and Drugs, Health & Wellbeing Directorate
Pilgrim Projects
POhWER
Pottergate Centre for Dissociation & Trauma
Powys Local Health Board
PrescQIPP NHS Programme
Primary Care Pharmacists Association
Primrose Bank Medical Centre
Priory Group
Prospect PBS Training Ltd
Public Health Agency
Public Health England
Public Health England Improving Health and Lives Learning Disabilities Observatory
Public Health Wales NHS Trust
Queen's University Belfast
Relate
Richmond Fellowship
Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust
Roche Products
ROCK Medical Communications
Roundhouse Care Ltd
Royal Berkshire NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners in Wales
Royal College of Midwives

Royal College of Obstetricians and Gynaecologists
Royal College of Pathologists
Royal College of Physicians
Royal College of Psychiatrists in Scotland
Royal College of Psychiatrists in Wales
Royal College of Radiologists
Royal College of Speech & Language Therapists
Royal College of Surgeons of England
Royal Free London NHS Foundation Trust
Royal Society of Medicine
Royal West Sussex NHS Trust
Rupanyup Hospital/Nursing Home
SANE
Sanofi
Scottish Intercollegiate Guidelines Network
Servier Laboratories Ltd
Sheffield Teaching Hospitals NHS Foundation Trust
SIFA Fireside
Social Anxiety UK
Social Care Association
Social Care Institute for Excellence
South Asian Health Foundation
South East Coast Ambulance Service
South Essex Partnership NHS Foundation Trust
South Essex Partnership University Foundation Trust
South Staffordshire and Shropshire Healthcare NHS Foundation Trust
South West Yorkshire Partnership NHS Foundation Trust
Southern Health Foundation Trust
Speak Out Against Psychiatry
Speaking Up
Spectrum Centre for Mental Health Research
St Andrews Healthcare
St Jude Medical UK Ltd.
St Mary's Hospital
St Mungo's
Staffordshire and Stoke on Trent Partnership NHS Trust
STEM4
Step4Ward Adult Mental Health
Stockport Clinical Commissioning Group
Suffolk County Council

Surrey and Border Partnership Trust
Survivors UK
Sussex Partnership NHS Foundation Trust
TACT
Tees, Esk and Wear Valleys NHS Trust
Teva UK
The Association for Clinical Biochemistry & Laboratory Medicine
The Association of the British Pharmaceutical Industry
The Bowlby Centre
The For All Healthy Living Centre
The Judith Trust
The National THORN Steering Group
The Orders of St John Care Trust
The Rotherham NHS Foundation Trust
The Samaritans
The Survivors Trust
The Wiltshire Trust
Together
Triumph over Phobia
Turning Point
UK Specialised Services Public Health Network
Unite the Union
United Kingdom Council for Psychotherapy
United Lincolnshire Hospitals NHS
United Response
University Hospital Birmingham NHS Foundation Trust
University Hospitals Birmingham
University of Edinburgh
University of Oxford Department of Psychiatry
Victims and Survivors Trust
Welsh Government
Welsh Scientific Advisory Committee
West London Mental Health NHS Trust
West Middlesex Hospital
Westminster Local Involvement Network
Whitstone Head Educational
Wigan Borough Clinical Commissioning Group
WISH A voice for women's mental health
Women's Support Network
Worcestershire Health and Care NHS Trust

YMCA
YMCA NI
York Hospitals NHS Foundation Trust
Young Muslims UK
Young People's Unit