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Issue 74 – July 2015

This month in Eyes on Evidence

[Symptom remission and quality of life in schizophrenia](#)

A retrospective study identified a link between symptom remission and improved quality of life in adults with schizophrenia who were on antipsychotic medication, with paid employment, social activity and drug adherence also positively influencing quality of life.

[Enhanced care and support at hospital discharge for older patients](#)

Two randomised controlled trials in Canada and the USA reported that enhanced care and support at discharge in addition to usual care did not reduce visits to the emergency department, hospital readmissions or deaths among older people compared with usual care.

[Using information on quality to make decisions about services](#)

A systematic review reported that people with long-term conditions or disabilities and their families sought information on the quality of health and social care services from multiple sources, in particular social networks. These groups tended to use general or subjective information rather than formal quality indicators to make decisions about providers.

[Long working hours and alcohol use](#)

A meta-analysis of cross-sectional and prospective data found that people who worked more than 40 hours a week were more likely to show risky alcohol use than people who worked fewer hours, although the increase was small. People who worked 55 hours a week or more were more likely to increase their alcohol use to levels that posed a health risk, but only 2 prospective published studies were available for this analysis.

[Risk of neuropsychiatric adverse events with varenicline](#)

A meta-analysis found no increase in the risk of suicide or attempted suicide, suicidal ideation or depression with varenicline compared with placebo. However, prescribers should be aware that the warnings on neuropsychiatric adverse events remain in place within the summary of product characteristics for varenicline.

[Evidence summaries from NICE's Medicines and Prescribing Programme](#)

NICE has recently published Medicines evidence commentaries on:

- Osteoarthritis and low back pain: evidence reviews raise further questions about the efficacy and safety of paracetamol
- Medicines optimisation: discontinuing statin therapy in palliative care
- Chronic obstructive pulmonary disease (COPD): indacaterol/glycopyrronium combination inhaler compared with tiotropium and formoterol in a randomised, non-inferiority study

Symptom remission and quality of life in schizophrenia



Overview: Schizophrenia is a major psychiatric disorder where a person's perception, thoughts, mood and behaviour are significantly altered ([NICE 2014](#)). The symptoms of schizophrenia are usually divided into 'positive symptoms', such as hallucinations (perception in the absence of any stimulus) and delusions (fixed or falsely held beliefs), and 'negative symptoms' (such as emotional apathy, lack of drive and social withdrawal). Schizophrenia is usually treated with medication, such as antipsychotic drugs, and tailored psychotherapy.

People with schizophrenia typically experience early signs of the disease followed by an acute episode marked by hallucinations, delusions and behavioural disturbances.

After resolution of the acute episode, symptoms diminish and often disappear for many people, although sometimes a number of negative symptoms remain.

Previous studies have had mixed findings as to how symptom remission affects quality of life in people with schizophrenia. Some studies suggest no link between a reduction in symptoms and quality of life ([Wunderink et al. 2007](#)), whereas others indicate that symptom remission improves quality of life ([Emsley et al. 2007](#)).

Current advice: The NICE guideline on [psychosis and schizophrenia in adults](#) recommends that people experiencing a first episode of psychosis should be offered oral antipsychotic medication in conjunction with psychological interventions (family intervention and individual cognitive behavioural therapy). Response to pharmacological treatment should be monitored and recorded regularly and systematically throughout treatment, as well as side effects and markers of physical health.

Pharmacological treatment may be considered to promote recovery and possible future care after an acute episode. Antipsychotic medication should be reviewed annually, including observed benefits and any side effects. Cognitive behavioural therapy should also be offered to assist in promoting recovery in people with persisting positive and negative symptoms and for people in remission.

The NICE pathway on [psychosis and schizophrenia](#) brings together all related NICE guidance and associated products on the conditions in a set of interactive topic-based diagrams.

New evidence: [Haro et al. \(2014\)](#) did a retrospective analysis of data from the [Schizophrenia Outpatients Health Outcomes \(SOHO\) study](#) to compare quality of life in people who experienced remission of schizophrenia symptoms and those who did not have remission.

The prospective, observational SOHO study aimed to assess outcomes in people with schizophrenia who were receiving antipsychotic drugs, in particular olanzapine, as outpatients. More than 10,000 people who were initiating or changing antipsychotic medication within the normal course of treatment for schizophrenia were recruited from 10 European countries. Participants underwent assessments of clinical status, social functioning, quality of life and pharmacological treatment at baseline and at 3, 6, 12, 18, 24, 30 and 36 months.

The analysis by Haro et al. (2014) looked at people who attended all SOHO follow-up visits or all but one visit. Symptom remission was defined as a score of 3 or less on the 7-point clinician-rated Clinical Global Impression-Schizophrenia scale, maintained for a period of 6 months or more, and the person must not have been hospitalised for their schizophrenia during this period. Quality of life was self-rated by participants using the European Quality of Life Questionnaire.

Among the 6516 people analysed (64% of the whole SOHO cohort), 38% were in symptomatic remission at 12-month follow-up, 45% were in remission at 18-month follow-up, and 52% were in remission at 36-month follow-up. Quality of life improved over time for all participants, including those who did not experience remission of their symptoms, although the improvement was greatest in people who were in remission for the full 36-month follow-up.

People who were in symptomatic remission had significantly better quality of life than people who were not in remission at each follow-up point from 12 months onwards ($p < 0.001$ for all). People in symptomatic remission were also more likely to be in a relationship, living independently, in paid employment and socially active ($p < 0.001$). Factors associated with good quality of life in people with schizophrenia were being in paid employment, being socially active, having good cognitive functioning, having better quality of life at baseline, and having good adherence to antipsychotic medication.

Limitations of this study include that the participants were people who were changing antipsychotic medication in an outpatient setting, so this group may not be representative of all people with schizophrenia. The validated scales used to assess remission and quality of life were subjective and may have introduced clinician or participant bias.

Commentary: “Evidence from studies investigating the relationship between symptomatic remission and quality of life has been inconsistent. The retrospective analysis of data from the SOHO study by Haro et al (2014) found a clear relationship between symptomatic remission and quality of life, with quality of life increasing over time for people who remained in remission over the 36-month study period.

“This study alone is not able to prove the relationship between symptomatic remission and self-rated quality of life, but is an important addition to our understanding. Its strengths include being based on data from a large prospective study that included a broad range of participants, had 36 months of follow-up and used a self-reported measure of quality of life. However, the findings may only be applicable to outpatients changing antipsychotic drug treatment.

“NICE guidance on psychosis and schizophrenia in adults recommends treatment with antipsychotic drugs, cognitive behavioural therapy for psychosis, and family interventions, because these interventions have been found to reduce symptoms, increase symptomatic remission and promote recovery. Improving quality of life is also an important aim in the treatment of people with psychosis and schizophrenia. The findings of this study do not suggest a change in practice to improve quality of life, because interventions aimed at the treatment of symptoms and prevention of relapse are already recommended in NICE guidance.” – **Dr Jonathan Mitchell, Consultant Psychiatrist, Sheffield Health & Social Care NHS Foundation Trust**

Study sponsorship: The Schizophrenia Outpatients Health Outcomes study was sponsored by Eli Lilly and Company. Haro et al. (2014) did not receive specific funding.

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Enhanced care and support at hospital discharge for older patients

Overview: An estimated 15–20% of readmissions 28–30 days after a patient has been discharged from hospital in the UK may be avoidable ([RAND Corporation 2012](#)). The emergency readmission rates for people aged over 75 years increased by 86% between 2002–03 and 2011–12 in England, considerably more than the 57% increase for people aged under 75 years ([Royal Voluntary Service 2014](#)). Readmission of patients is associated with costs for hospitals.



Several initiatives have aimed to reduce readmissions among elderly patients by targeting the hospital discharge period. One approach is the 'virtual ward', which provides people at high risk of readmission with a period of intensive, multidisciplinary management in the community using the systems, staffing and daily routines of a hospital ward ([Lewis et al. 2013](#)). Another approach is 're-engineered' discharge, where a nurse and clinical pharmacist coordinate hospital discharge, educate patients and reconcile medications ([Jack et al. 2009](#)).

Current advice: Individual hospitals tend to have their own policies and arrangements for discharging patients ([NHS Choices 2015](#)). Generally, patients in hospital who are due to leave should be given a discharge assessment and a care plan outlining the ongoing health and social care support they need. Patients should also be given a letter for their GP and enough drugs for the next 7 days.

The NICE guideline on [patient experience in adult NHS services](#) recommends effective coordination and prioritisation of care for patients who use a number of different services (for example, services in both primary and secondary care). This should include clear and timely exchange of patient information between healthcare professionals (particularly at the point of any transitions in care).

The NICE guideline on [medicines optimisation](#) recommends that relevant information about medicines should be shared with patients, and their family members or carers, where appropriate, and between health and social care practitioners when a person moves from one care setting to another. Medicines reconciliation should be carried out in primary care for all people who have been discharged from hospital or another care setting.

NICE is currently preparing social care guidance on [transition between inpatient hospital settings and community or care home settings for adults with social care needs](#) (anticipated publication date November 2015).

The NICE pathways on [patient experience in adult NHS services](#) and [medicines optimisation](#) bring together all related NICE guidance and associated products in sets of interactive topic-based diagrams.

New evidence: Two randomised controlled trials investigated whether enhanced care and support for older people at hospital discharge affected the likelihood of subsequent hospital visits compared with usual discharge care.

[Dhalla et al. \(2014\)](#) assessed how a 'virtual ward' intervention affected readmissions and mortality in older people at high risk of readmission. A total of 1923 patients aged 71 years on average were recruited on

discharge from a general internal medicine ward at 4 study sites in Canada. People randomised to the usual care group (n=965) received a written discharge summary, a prescription when indicated, counselling from a doctor or other healthcare professional, arrangements for home care as needed, and recommendations for appointments or follow-up care.

People randomly assigned to the virtual ward group (n=967) received usual care plus individualised post-discharge care by a team of care coordinators, pharmacists, nurses, doctors and clerical assistants. Patients received care at home and in the hospital clinic where the team was based, and had access to a telephone helpline.

No significant difference was observed between the 2 study groups in the composite primary outcome of readmission to any hospital or death within 30 days of discharge. During the first 30 days after discharge, 24.6% of patients assigned to usual care and 21.2% of patients assigned to the virtual ward had been readmitted to hospital or died (absolute difference=3.4%, 95% confidence interval [CI] -0.3% to 7.2%, p=0.09).

Limitations of this study include that many patients who met the eligibility criteria were not recruited because they were discharged on holidays, evenings or weekends. In addition, a virtual ward model of care may have different effects in a differently structured healthcare system.

[Goldman et al. \(2014\)](#) assessed the effects of nurse-led in-hospital discharge support with telephone follow-up, on emergency department visits and readmissions among 700 ethnically and linguistically diverse older patients. People aged 55 years or older who spoke English, Spanish or Chinese were recruited from a single US hospital that dealt with a large number of uninsured and vulnerable patients.

People randomly assigned to usual care (n=353) received discharge instructions and, if required, a medication supply and social care support after discharge. People randomly assigned to discharge support (n=347) also received visits and disease-specific education in their own language from a nurse before discharge and within 24 hours after discharge. People in the discharge support group had follow-up telephone calls on day 1–3 and day 6–10 after discharge and had access to a telephone helpline.

People in the 2 study groups had similar numbers of visits to the emergency department and hospital admissions at 30, 90 and 180 days after discharge. The number of emergency department visits or readmissions in the intervention and usual care groups were 112 versus 89 events at 30 days (hazard ratio [HR]=1.26, 95% CI 0.89 to 1.78, p=0.19), 238 versus 203 events at 90 days (HR=1.21, 95% CI 0.91 to 1.62, p=0.19), and 392 versus 370 events at 180 days (HR=1.11, 95% CI 0.86 to 1.43, p=0.44).

The authors of this study note that not all readmissions and visits to the emergency department were recorded and the rates were lower than predicted, which decreased the power of the analysis.

Commentary: “The NHS in England, like many health systems around the world, has been grappling with how to reduce emergency hospital readmissions for a number of years. Sadly, when it comes to developing guidance on how to do this, there is little robust evidence on what actually works. Set against this background, the Dhalla et al. (2014) and Goldman et al. (2014) studies are welcome additions to our knowledge.

“Both studies are randomised controlled trials, which provide the best way of assessing whether an intervention is effective. Neither study found evidence that the interventions they were testing worked. This suggests that the NHS should be cautious about wide-scale adoption of virtual wards or nurse-led discharge support as solutions to the problem of emergency readmissions.

“However, as the studies were undertaken in hospitals in Canada and the USA, it may be that their findings are not directly applicable to the NHS. It may be that in some circumstances, one or both of these interventions might be effective in some NHS hospitals. It may thus be reasonable for policy makers and managers to trial virtual wards or nurse-led discharge support in the context of well-designed local pilots or research studies.

“It is also important to remember that these studies tried to test if one specific intervention made a big

enough difference on outcomes to be detectable in a study setting. However, the history of quality improvement in healthcare suggests that successful improvement rarely comes down to single 'magic bullet' interventions. It may be that combining a bundle of appropriate interventions produces results that are more than the sum of their parts. Examining the effectiveness of such bundles (in pilots or research studies) may help NHS hospitals learn how best to reduce readmissions." – **Dr Anas El Turabi, British primary care physician and Frank Knox Fellow and Doctoral Candidate in Health Policy at Harvard University**

Study sponsorship: Dhalla et al. (2014) was funded by the Canadian Institutes of Health Research, the Ontario Ministry of Health and Long-Term Care, the Green Shield Canada Foundation, the University of Toronto Department of Medicine and the Academic Funding Plan Innovation Fund. Goldman et al. (2014) was funded by the Gordon and Betty Moore Foundation, the Agency for Healthcare Research and Quality and the US National Institutes of Health.

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Using information on quality to make decisions about services



Overview: Offering people choice in who provides their health or social care has been shown to improve service quality and lead to better health outcomes ([Cooper et al. 2011](#)). In England, the [Health and Social Care Act 2012](#) enshrined in law the requirement for NHS organisations to protect and promote the right of patients to make choices about treatment or other healthcare services. The [NHS Choice Framework](#) outlines the circumstances where people have a legal right to choose their treatment and care in the NHS. In addition, [personal budgets](#) from local authorities allow people to choose how they would like to receive social care and support.

Information on the quality, cost and availability of services is important to allow people to make decisions about health or social care. However, patients may have limited awareness of information on the quality of services and may not use such information in making decisions ([Ketelaar et al. 2011](#)).

Current advice: The NICE guideline on [patient experience in adult NHS services](#) recommends that patients, and their family members and/or carers where appropriate, should be given information, and the support they need to make use of the information, in order to promote their active participation in care and self-management.

Support should be offered to patients who are considering their diagnosis, prognosis and treatment options. The principles of shared decision making should be used, including ensuring that the patient is aware of the options available and the risks, benefits and consequences of these. Whether or not the patient understands the information should be clarified.

The NICE guideline on [medicines optimisation](#) recommends that many people wish to be active participants in their own healthcare, and to be involved in making decisions about their medicines. The best available evidence should be used when making decisions with or for individuals.

The NICE pathways on [patient experience in adult NHS services](#) and [medicines optimisation](#) bring together all related NICE guidance and associated products in sets of interactive topic-based diagrams.

New evidence: [Turnpenny and Beadle-Brown \(2015\)](#) did a systematic review of evidence on how people with long-term conditions or disabilities and their families used information about service quality to make decisions about health and social care providers. Of the 13 studies included, 5 considered decision-making in healthcare, such as choosing a facility for elective orthopaedic surgery, and 7 considered decisions about social care, such as selecting a nursing home (1 study assessed both health and social care). The information available included formal quality reports (for example, inspection reports), information about the characteristics of a service or provider (for example, number and qualifications of staff) and informal reports about quality (for example, personal experience).

The review found that people with long-term conditions or disabilities used a wide variety of sources for information on the quality of health and social care; for example, advertising, information from service providers, and the internet. Medical professionals and informal networks were trusted as sources of information on quality. However, people generally had very little awareness of formal sources of information about quality, such as inspection reports, and very limited knowledge about indicators of a quality service.

When the type of information on quality was considered, written information presented as percentages and graphs was valued, as was verbal information. Consumer satisfaction was found to be an important type of information on quality, followed by inspection reports and formal quality indicators. Experiential and subjective information (such as user ratings) was highly valued and trusted.

People who used information on quality applied it in a variety of ways determined by their personal circumstances: some used personal key indicators, others considered all indicators, and some used exclusion criteria. However, decision-making on health and social care providers was often based on general information (such as location) or subjective impressions (such as perceived reputation). People tended to use their own definition of quality, such as friendliness of staff or cleanliness, when formal information was lacking or when quality information was difficult to interpret.

A limitation of this review is that studies in countries other than the UK were included, and differences in the organisation of health and social care in different countries could have influenced the findings. In addition, few details were given of the search strategy, secondary studies and grey literature were not included, and publication bias was not assessed.

Commentary: “This is a well-executed systematic review that addresses access and use of ‘quality information’ by people with long-term conditions and their families. The findings appear robust, if not that surprising – that is, that people use multiple sources of information on quality and rely more on general information and personal networks than ‘official’ sources. However, the evidence adds to our understanding of why certain sources are not used, in particular highlighting the importance of trust and timeliness.

“The evidence usefully highlights the challenges that service users face, especially when under time pressure, in appropriating ‘official’ information on quality so that they can actually use it to inform their personal decisions. This finding is important because it suggests that no matter how robust formalised quality information is, there will still be challenges of use. This information is necessarily generic, speaking to populations rather than individuals. This study suggests that achieving the benefits of choice requires not just more and improved sources of information, but more effective means, beyond just personal networks, to help people with long-term conditions and their families translate information on quality so that it is appropriate for their personal circumstances. Improving professional support aimed at helping service users actually use, rather than just access, quality information may reduce the transition and psychological costs associated with ill-informed choices.

“The review has some limitations that, while acknowledged, could be further addressed. It includes studies from countries (UK, USA and Netherlands) that have very different health systems. The authors could have considered some analysis of whether there were country differences in the reporting of findings or whether contextual contingencies were noted in these studies. Finally the definition of ‘quality information’ is very broad, including sources (for example, personal appraisal of the décor and furnishing of care homes) that might arguably relate to things other than quality of care.” – **Professor Jacky Swan, Professor in Organisational Behaviour, University of Warwick**

Study sponsorship: Department of Health.

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Long working hours and alcohol use

Overview: Government guidelines on alcohol recommend that men should not regularly drink more than 3 to 4 units of alcohol per day and women should not regularly drink more than 2 to 3 units per day ([Department of Health 2015](#)). However, 34% of men and 28% of women in Great Britain exceed these limits on their heaviest drinking day of the week ([Office for National Statistics 2013](#)). Heavy drinking is defined as drinking more than 8 units of alcohol for men and more than 6 units for women. In 2011, the proportion of men drinking more than 8 units on their heaviest drinking day was 18% and the proportion of women drinking more than 6 units was 12%.

The European Working Time Directive limits working hours for people in EU countries to 48 hours a week to protect workers' health and safety ([European Commission 2003](#)). Working long hours has been shown to increase the risk of adverse health outcomes such as depression, anxiety and sleep deprivation ([Bannai and Tamakoshi 2014](#)). Long working hours may also increase the likelihood of risky drinking ([Gibb et al. 2011](#)).



Current advice: The NICE public health guideline on [alcohol-use disorders: preventing harmful drinking](#) recommends that NHS professionals should routinely carry out alcohol screening as an integral part of practice. Screening involves identifying people who are not seeking treatment for alcohol problems but who, in the view of the professional, may have an alcohol-use disorder. A validated alcohol questionnaire should be used with the adults being screened.

Adults who have been identified via screening as drinking a hazardous or harmful amount of alcohol should be offered a session of structured brief advice on alcohol.

The NICE pathway on [alcohol-use disorders](#) brings together all related NICE guidance and associated products on the conditions in a set of interactive topic-based diagrams.

New evidence: [Virtanen et al. \(2015\)](#) carried out a meta-analysis to assess whether long working hours were associated with using alcohol at a level that might pose a health risk. The authors identified 36 relevant published studies, 34 of which were cross-sectional and 2 prospective. This analysis also included unpublished individual participant data identified from a meta-analysis consortium and open access data collections: 27 sets of cross-sectional data and 18 sets of prospective data. The published and unpublished data were pooled into two groups for meta-analysis: cross-sectional data (61 studies, n=333,693) and prospective data (20 studies, n=100,602).

The published studies variously defined long working hours as 45 hours a week or more, more than 40 hours a week, or 'frequent overtime'. Alcohol use was based on self-reported frequency, and definitions of risky alcohol use varied considerably. The unpublished studies split working hours into less than 35 hours a week, 35–40 hours a week, 41–48 hours a week, 49–54 hours a week, and 55 hours a week or more. Risky alcohol use was defined as more than 14 drinks a week for women and more than 21 drinks a week for men.

Pooled analysis of the published and unpublished cross-sectional data found that long working hours were associated with a small increase in the likelihood of risky alcohol use (odds ratio [OR]=1.11, 95% confidence interval [CI] 1.05 to 1.18). The published cross-sectional studies were very heterogeneous, but meta-regression models of sex, study location, sociodemographic and population variables could not explain the heterogeneity.

Pooled analysis of the published and unpublished prospective data found that among people who used alcohol at safe levels at baseline, those who worked at least 55 hours a week were more likely to develop risky alcohol use than those who worked 35–40 hours a week (OR=1.12, 95% CI 1.04 to 1.20). Working 49–54 hours a week was associated with a similar risk of onset of risky alcohol use (OR=1.13, 95% CI 1.02 to 1.26).

Limitations of this analysis include that only 2 prospective published studies were available and most studies used self-reported data on working hours and alcohol use. All the included studies were observational, which limits the generalisability of these results.

Commentary: “As noted above, interpreting the literature on health effects of alcohol use is especially difficult because researchers, in the natural course of events, choose very different definitions of what constitutes ‘heavy’, ‘excessive’ or ‘risky’ alcohol use. In addition, most studies rely on personal recall by participants. For some drinkers, recall may be simple (for example, men who go to the pub every night and order 2 pints of beer), but for others (for example, regular drinkers of varying amounts of beer, spirits and wine) it may not.

“The findings of this new meta-analysis may have public health relevance if they do reflect a true causal relationship – that is, long hours led to increased alcohol use, and not, for example, that loneliness led to working long hours and increased alcohol use. But it is difficult to see how the findings can be incorporated into clinical practice, because the size of the effect at a personal level would be very small.

“The review is a reminder that as the size of a meta-analysis increases, smaller and smaller effects will become statistically significant, such that in an infinitely large study, the tiniest difference will be statistically significant. Epidemiological findings should be interpreted cautiously because it is so easy to be misled by observational studies, particularly when the findings refer to small effects.” – **Professor Tom Sorahan, Professor of Occupational Epidemiology, University of Birmingham**

Study sponsorship: This study was not funded.

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Risk of neuropsychiatric adverse events with varenicline



Overview: Varenicline is licensed for smoking cessation in adults. According to the [summary of product characteristics](#), smokers should set a date to stop smoking, and treatment with varenicline should start 1 to 2 weeks before this date and continue for 12 weeks in total. For people who have stopped smoking after 12 weeks, an additional 12-week treatment course may be considered for maintaining abstinence.

Varenicline may also be used for a gradual approach to stopping smoking for people who are unable or unwilling to stop abruptly. Smoking should be reduced during the first

12 weeks of varenicline treatment and stopped by the end of that period. Treatment should subsequently be continued for a further 12 weeks. The [summary of product characteristics](#) highlights that smoking cessation therapies are more likely to succeed in people who receive additional advice and support.

In 2008, the MHRA advised that [depression](#) and [suicidal thoughts and behaviour](#) had been reported in people using varenicline, including those with no pre-existing psychiatric conditions. In 2009, a UK cohort study found no clear evidence that varenicline was associated with an increased risk of fatal or non-fatal self-harm, depression or suicidal thoughts ([Gunnell et al. 2009](#)). The MHRA reviewed this study and commented that it provided [some reassurance about the risk of varenicline on suicidal behaviour](#). However, the warnings in the summary of product characteristics for varenicline were not amended.

Current advice: NICE recommends that [varenicline](#) is a possible treatment to help smokers who want to stop smoking. It should normally be used only as part of a programme that includes advice from a healthcare professional or other types of support.

Clinicians should be aware of the possible emergence of significant depressive symptoms in people using varenicline as part of a smoking cessation attempt. Varenicline should be stopped immediately if agitation, depressed mood or changes in behaviour or thinking are observed that are of concern for the doctor, the user, family or caregivers, or if the user develops suicidal ideation or suicidal behaviour. See the [summary of product characteristics](#) for more information on the neuropsychiatric adverse effects of varenicline.

The NICE guideline on [smoking cessation services](#) provides more information on the use of nicotine replacement therapy, varenicline and bupropion to aid smoking cessation, along with giving advice, encouragement and support, or referral to a smoking cessation service. The NICE pathway on [smoking](#) brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.

New evidence: A systematic review and meta-analysis has assessed the risk of neuropsychiatric adverse events and death in published placebo-controlled, randomised controlled trials (RCTs) of varenicline 1 mg twice daily ([Thomas et al. 2015](#)). Of the 44 studies identified, 39 were included in the meta-analysis (n=10,761).

Two people in the varenicline group (n=5817) committed suicide, and 2 people in each of the varenicline group and the placebo group (n=4944) attempted suicide. There was no significant difference between the groups in the primary outcomes of risk of suicide or attempted suicide (odds ratio [OR]=1.67, 95% confidence interval [CI] 0.33 to 8.57; 31 RCTs, n=9830), suicidal ideation (OR=0.58, 95% CI 0.28 to 1.20; 20 RCTs, n=4990) or depression (OR=0.96, 95% CI 0.75 to 1.22; 31 RCTs, n=9843). There was also no difference between the groups in the risk of death, irritability, aggression or somnolence. Compared with placebo, varenicline was associated with an increased risk of sleep disorders, insomnia, abnormal dreams and fatigue, but a reduced risk of anxiety.

Subgroup analyses found no evidence for a variation in depression and suicidal ideation by age, gender, ethnicity, smoking status, presence or absence of psychiatric illness, or type of study sponsor.

The authors concluded that these results provide some reassurance for users and prescribers about the neuropsychiatric safety of varenicline. However, the study has several limitations. For example, it was not possible to determine whether differences in adverse events were because of greater smoking cessation rates in the varenicline group compared with placebo. Also, biases such as reporting and publication bias could not be excluded.

Commentary: "This study provides a robust analysis of the risk of neuropsychiatric adverse events associated with varenicline, in the context of people eligible for participation in clinical trials. This backs up the evidence for no association of varenicline with neuropsychiatric events from observational studies.

"However, it should be noted that included trials did vary in their exclusion criteria, with some excluding people with a history of depression, suicidal ideation or suicide attempts. Additionally, the authors note the small number of attempted suicides and suicides mean an effect of varenicline on suicide rates cannot be ruled out. Variability of definitions, and detection, of suicidal ideation and suicide in both RCTs and

observational studies is a known problem.

“The spontaneous case reports that led to the initial concerns over varenicline have multiple confounding factors, such as the potential neuropsychiatric effects of smoking cessation itself, concomitant medicines, alcohol, and a predisposition to depression. However, the rare possibility that varenicline might cause severe neuropsychiatric reactions in susceptible individuals cannot be eliminated. Nevertheless, this meta-analysis provides additional reassurance that the overall risk of suicide with varenicline is negligible in the majority of people without potential risk factors.

“This short-term rare risk also needs to be balanced with the long-term risks associated with smoking, as well as the risks and effectiveness of other smoking cessation therapies. This study should reassure us that varenicline can be used confidently, as per current NICE guidance. However, prescribers should be aware of the manufacturer’s warnings, and counsel people about the potential for rare neuropsychiatric symptoms, particularly in those with risk factors (such as a history of psychiatric illness). People should be informed in a balanced way about the evidence, but also encouraged to report any concerns they may have.” – **Dr Anthony Cox, Senior Lecturer in Clinical Pharmacy, University of Birmingham**

Study sponsorship: This study was not funded.

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Evidence summaries from NICE’s Medicines and Prescribing Programme

NICE has recently published the following Medicines evidence commentaries:

[Osteoarthritis and low back pain: evidence reviews raise further questions about the efficacy and safety of paracetamol](#)

This evidence commentary reviews 2 systematic reviews on the safety and effectiveness of paracetamol for hip or knee osteoarthritis and low back pain in the short term.

[Medicines optimisation: discontinuing statin therapy in palliative care](#)

This evidence commentary reviews a randomised controlled trial that considered the clinical impact and safety of discontinuing statins in people with advanced, life-limiting illness.

[Chronic obstructive pulmonary disease \(COPD\): indacaterol/glycopyrronium combination inhaler compared with tiotropium and formoterol in a randomised, noninferiority study](#)

This evidence commentary reviews a double-blind randomised controlled trial on the non-inferiority of indacaterol/glycopyrronium to tiotropium plus formoterol in improving health-related quality of life of people with moderate to severe COPD.

Medicines evidence commentaries form part of NICE’s [Medicines Awareness Service](#) and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. These commentaries were published in NICE’s [Medicines Awareness Weekly](#) service and are available online in [NICE Evidence Search](#).

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