NICE National Institute for Health and Care Excellence

Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Major depressive disorder in older people: antidepressants

A network meta-analysis found that sertraline, paroxetine and duloxetine were statistically significantly more effective than placebo in people aged 60 years or older with major depressive disorder. Duloxetine was statistically significantly more effective than citalopram, fluoxetine and escitalopram, and paroxetine was more effective than fluoxetine and escitalopram. However, the study has limitations and the clinical importance of the findings is unclear. Also, duloxetine and venlafaxine caused statistically significantly more dizziness than placebo and little data were available for other adverse effects. Clinicians should continue to follow NICE guidance on depression in adults and, if an antidepressant is needed, usually prescribe a generic selective serotonin reuptake inhibitor first-line, taking into account the risk of drug interactions, adverse effects and discontinuation symptoms particularly in older people.

Overview and current advice

The NICE guideline on depression in adults (currently being updated; anticipated publication date May 2017) advises that antidepressants should not be used routinely to treat persistent subthreshold depressive symptoms or mild depression, but can be considered for people with:

- a past history of moderate or severe depression or
- initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least 2 years) or
- subthreshold depressive symptoms or mild depression that persist(s) after other interventions.

People with moderate or severe depression should be offered a combination of antidepressant medication and a high-intensity psychological intervention, such as cognitive behavioural therapy or interpersonal therapy. If an antidepressant is considered necessary, NICE advises that it should normally be a generic selective serotonin reuptake inhibitor (SSRI), because SSRIs are equally as effective as other antidepressants and have a favourable risk–benefit ratio. The NICE guideline on depression in adults with a chronic physical health problem (such as cancer, heart disease, diabetes, or a musculoskeletal, respiratory or neurological disorder) also advises that a generic SSRI should be considered first-line. Citalopram or sertraline should be considered in people taking other medications because they are less likely to interact with other drugs.

When prescribing antidepressants for older people, NICE recommends that an age-appropriate dose should be used, taking into account the effect of general physical health and concomitant medication

on pharmacokinetics and pharmacodynamics. The person should be carefully monitored for side effects.

The NICE Pathway on depression brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The NICE clinical knowledge summary on depression provides a useful overview of the condition and its management.

New evidence

A systematic review and meta-analysis (Thorlund et al. 2015[1]) has considered the comparative efficacy and safety of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) in people aged 60 years or older with a primary diagnosis of major depressive disorder. It included randomised controlled trials (RCTs) comparing these drugs with placebo or another antidepressant for at least 6 weeks. Network meta-analyses were used to compare the relative effects of treatments that have not been compared with each other directly in head-to-head trials. The efficacy outcome considered was partial response to treatment, defined as a 50% reduction or more in depression score from baseline (Hamilton Depression Rating Scale or Montgomery–Asberg Depression Rating Scale). Safety outcomes included dizziness, syncope, vertigo, loss of consciousness and falls.

Fifteen RCTs (n=4588) were identified, which assessed 7 SSRIs and SNRIs (sertraline, venlafaxine, citalopram, paroxetine, duloxetine, fluoxetine and escitalopram) over 6–12 weeks. Twelve RCTs reported on partial response, 12 reported on dizziness, 3 reported on falls and 2 reported on syncope. No data were available for vertigo or loss of consciousness. Network meta-analyses could be undertaken only for partial response and dizziness. The numbers of people in each analysis were not reported.

Only sertraline, paroxetine and duloxetine were found to be statistically significantly more effective than placebo in terms of partial response (relative risk [RR] 1.28, 95% confidence interval [CI] 1.07 to 1.51; RR 1.48, 95% CI 1.27 to 1.75 and RR 1.62, 95% CI 1.26 to 2.05 respectively). For this outcome, duloxetine was also found to be statistically significantly more effective than citalopram, fluoxetine and escitalopram (RR 1.53, 95% CI 1.01 to 2.46; RR 0.66, 95% CI 0.51 to 0.88 and RR 0.73, 95% CI 0.55 to 0.98 respectively).* Paroxetine was found to be statistically significantly more effective than fluoxetine and escitalopram (RR 0.72, 95% CI 0.59 to 0.88 and RR 0.80, 95% CI 0.63 to 0.99 respectively).* No significant differences were seen for other comparisons of SSRIs or SNRIs with placebo or other antidepressants.

Venlafaxine and duloxetine caused statistically significantly more dizziness than placebo (RR 3.18, 95% CI 1.60 to 6.03 and RR 2.94, 95% CI 1.03 to 8.37 respectively). Venlafaxine also caused significantly more dizziness than sertraline and fluoxetine (RR 2.87, 95% CI 1.23 to 6.52 and RR 0.41, 95% CI 0.21 to 0.81 respectively).* No significant differences were seen for other comparisons versus placebo or active comparators.

In the 3 RCTs reporting falls, 1 fall was seen in a sertraline group (n=360), 2 were seen in a paroxetine group (n=334), 1 was seen in a duloxetine group (n=201) and no falls were seen in the 3 placebo groups. In 2 RCTs, syncope was reported in 1 person taking sertraline (n=360), 1 person taking escitalopram (n=129) and 1 person taking placebo (n=134).

The systematic review and meta-analysis has limitations. Publication bias may have affected the analyses, although Thorlund et al. (2015) noted that most of the included RCTs were not initiated by the pharmaceutical industry. The authors also considered that the quality of reporting of trials was variable, adverse events were inadequately captured and probably under-reported, and the majority of comparisons were based on 1 RCT only. Sample sizes ranged from 27 to 728 people and comparisons based on smaller sample sizes are likely to lack statistical power. Follow-up was only 6–

12 weeks, which may be insufficient to adequately assess safety of antidepressants. Remission was not included as an outcome because it was infrequently recorded in RCTs and the low number of remission events would have reduced the statistical power of comparisons.

Commentary

Commentary provided by the Medicines and prescribing programme, NICE

The network meta-analyses by Thorlund et al. (2015) showed that some of the antidepressants studied were statistically significantly more effective than placebo or other antidepressants in people aged 60 years or older. However, as the study authors point out, the clinical significance of the findings should be considered. Clinical significance indicates the degree to which the effect of a drug or other intervention translates to a meaningful improvement in symptoms for patients. The benefits of antidepressants might be small when averaged over the population; nevertheless, a subset of older adults may see clinically important improvements in symptoms. Conversely, a subset may see clinically important harms.

The full NICE guideline on depression in adults had similar findings based on a network meta-analysis (Cipriani A et al. 2009[2]) of 12 newer antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine) for treating major depression in adults of all ages. The Guideline Development Group concluded that, although there may be differences in efficacy and tolerability between individual drugs, given the modest sizes of the effects and some methodological uncertainties, there was sufficient doubt about the clinical importance of the differences to justify not developing recommendations for specific drugs. However, differences between drugs relating to tolerability and safety were highlighted in the guidance where relevant.

The NICE guideline on depression in adults recommends that, if an antidepressant is considered necessary, it should normally be a generic SSRI because SSRIs are equally effective as other antidepressants and have a favourable risk–benefit ratio. When prescribing antidepressants for older people, NICE recommends that an age-appropriate dose should be used, taking into account the effect of general physical health and concomitant medication on pharmacokinetics and pharmacodynamics. People should be carefully monitored for side effects. The NICE guideline on depression in adults with a chronic physical health problem makes similar recommendations around drug treatment of depression but also lists some interactions of SSRIs and notes that they may result in or exacerbate hyponatraemia, especially in older people.

SSRIs are associated with an increased risk of bleeding, especially in older people and in people taking other drugs that have the potential to damage the gastrointestinal mucosa or interfere with clotting. The NICE guideline on depression in adults recommends that co-prescription of a gastroprotective drug should be considered in older people who are also taking non-steroidal anti-inflammatory drugs or aspirin. The NICE guideline on depression in adults with a chronic physical health problem recommends alternative antidepressants for people taking NSAIDs and aspirin. Many older people have comorbidities and may be taking several drugs. Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs.

When prescribing antidepressants other than SSRIs, the NICE guideline on depression in adults advises that the increased likelihood of the person stopping treatment because of side effects (and the consequent need to increase the dose gradually) with venlafaxine, duloxetine and tricyclic antidepressants should be taken into account. Also, the specific cautions, contraindications and monitoring requirements for some drugs should be considered, including for example, the potential for higher doses of venlafaxine to exacerbate cardiac arrhythmias and the need to monitor the person's

blood pressure, and the possible exacerbation of hypertension with venlafaxine and duloxetine. See the guidelines for more details on prescribing SSRIs and SNRIs.

Study sponsorship

The study was funded by Pfizer.

* The **relative risks** (RRs) for outcomes are presented as numbers both above and below zero, depending on which drug in the comparison was considered first. If the **confidence intervals** do not cross 1 (which would mean any differences were not statistically significant and outcomes were equally likely in both groups), a RR of less than 1 means the outcome is **less** likely in the first group. A RR of more than 1 means the outcome is **more** likely in the first group. For example, in the network meta-analyses for partial response, duloxetine was compared with citalopram and the RR was 1.53, meaning partial response was statistically significantly more likely with duloxetine compared with citalopram. By comparison, fluoxetine was compared with duloxetine and the RR was 0.66 meaning partial response was statistically significantly less likely with fluoxetine compared with duloxetine. In other words, duloxetine was statistically significantly more effective than citalopram and fluoxetine (and escitalopram RR 0.73).

References

1. References Thorlund K, Druyts E, Wu P et al. (2015) Comparative Efficacy and Safety of Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors in Older Adults: A Network Meta-Analysis. Journal of the American Geriatrics Society 63:1002–9
2. Cipriani A, Furukawa, TA, Salanti G et al. (2009) Comparative efficacy and acceptability of 12 new generation antidepressants: a multiple treatments meta-analysis. The Lancet 373:746–58

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