Psychiatria Danubina, 2013; Vol. 25, Suppl. 2 , pp 286–290 *Conference paper*

SERTRALINE AND MIRTAZAPINE AS GERIATRIC ANTIDEPRESSANTS

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SUMMARY

Background: *Depression within the geriatric patient population is an important issue as it is associated with increased mortality. Such depression may have a different aetiology to that in younger patients and be associated with comorbid chronic physical health problems or cognitive impairment. However, there is no specific UK guideline for the treatment of depression within elderly patients. The first-line pharmacological treatment recommended by the National Institute for Health and Care Excellence (NICE) is to use a serotonin-selective reuptake inhibitor (SSRI). Unfortunately these can have significant side-effects in the elderly such as hyponatraemia. Sertraline is one such SSRI commonly used in the geriatric population. Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSa) is seeing increasing usage as an alternative agent. Here we evaluate the role of using the NaSSA in place of the SSRI and how such drugs may be cross-titrated.*

Methods: *PubMed and an internet search engine were used to identify relevant studies and information sources.*

Conclusions: *Limited evidence suggests that for certain elderly patients, mirtazapine may be preferable to sertraline for treatment of depression. It may also be more cost-effective in patients who have dementia. The choice is highly dependent upon individual co-morbidities and subsequent polypharmacy. If required, sertaline can be cross-titrated to mirtazapine.*

Key words: *depression – geriatrics – sertraline - mirtazapine*

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INTRODUCTION

The prevalence of major depression in the population aged greater than 60 years is estimated from 2-5% (Mottram et al. 2006) with as many as 16% of over 65s reporting significant depressive symptoms (Blazer 2009). Multiple reports suggest that such depression is associated with greater mortality (Schulz et al. 2002, Gallo et al. 2013). A larger proportion of the older population suffer from physical health problems and this is also increases risk of depression; as a whole around 20% of people with chronic health problems suffer depression (NCCMH 2010).

Consequently, the recognition and treatment of geriatric depression, as well as its prevention, is of great significance. Antidepressant pharmacotherapy is commonly used to help symptoms of depression. In the UK, whilst there are several guidelines covering antidepressant treatment amongst adults (NICE 2009a), young people (NICE 2005) and adults with a chronic physical health problem (NICE 2009b) there are only brief comments addressing the added complexities in pharmacotherapy for the elderly, such as polypharmacy and comorbidities. The aetiology of depression amongst elderly patients may also differ to younger patients, in particular with regard to vascular insults (Alexopoulos & Kelly, Jr. 2009) and endocrine changes (Blazer 2009). Nonetheless, two Cochrane reviews (Mottram et al. 2006, Wilson et al. 2001) indicated that antidepressant drugs are still effective amongst elderly patients, also noting that tricyclic antidepressants may have less desirable side-effect profiles. Serotonin-selective reuptake inhibitors (SSRIs) are the first-line agents recommended by the National Institute for Health and Care Excellence (NICE) (NICE 2009a). Of the drugs from this class, sertraline has been suggested to be an appropriate first choice due its lesser side-effect profile when compared to other SSRIs (Muijsers et al. 2002), as well as its approval for use with comorbid cardiac disease following myocardial infarction (UKMi 2012a).

There are now however so-called ‘atypical’ antidepressants appearing in hospital formularies such as the noradrenergic and specific serotonergic antidepressant (NaSSa) mirtazapine. The effectiveness of mirtazapine in treating depression appears comparable to the SSRIs and it also has a small side-effect profile (Antilla & Leinonen 2001). Therefore it is sometimes considered for use as an alternative agent if the first antidepressant started is ineffective.

Here we present a mini-review of current literature regarding use of sertraline and mirtazapine. Firstly we shall review current guidance in the UK regarding pharmacotherapy for depression in the elderly, before considering specific issues that may favour prescription of one drug over the other. Finally we summarise guidelines on the safe cross-titration of sertraline to mirtazapine.

METHODS

A PubMed search using MeSH terms “mirtazapine sertraline geriatrics” across all fields yielded only one result which was a general review of pharmacological treatment of depression amongst elderly patients. Changing the search to “mirtazapine sertraline elderly”

produced 57 results, 9 of which were relevant. Broadening further still to "mirtazapine sertraline" gave 173 results including 4 additional relevant articles. Where appropriate we also used an internet-based search engine targeted to find details of national guidelines such as those from NICE as well as other individual studies of interest.

DISCUSSION

Current Guidance

The current UK guidance from NICE (applicable to adults) suggests that if wishing to start pharmacological treatment, the first class of agent to use should be an SSRI. If symptoms fail to improve after ~6 weeks then another drug can be tried (NICE 2009a). However, the guidance issued relating to adults with a chronic physical health problem specifically cautions the use of SSRIs in the elderly due to the increased associated risk of hyponatraemia. Nonetheless, it does still suggest citalopram or sertraline as possible initial choices based upon them having fewer drug interactions than other SSRIs. A number of other cautions applied to SSRI usage are listed in Table 1 (NICE 2009b).

Table 1. Situations in which NICE guidance cautions SSRI usage (NICE 2009b)

Increased risk of bleeding (concomitant non-steroidal anti-inflammatory drug or aspirin use)
Patients on warfarin or herapin
Patients using triptan-class drugs
Patients on monoamine oxidase B inhibitors
Elderly patients in whom SSRIs may precipitate hyponatraemia

For elderly patients, of these two drugs sertraline may be a more favourable choice. It is the preferred SSRI following myocardial infarction and can be used at higher relative doses than citalopram due to the latter's association with QT interval prolongation (UKMi 2012a). Older patients are perhaps more likely to be taking other drugs which may already predispose to a longer QT interval. The NICE guidance suggests sertraline is safe for use in conjunction with flecainide or propafenone (NICE 2009b) which some other SSRIs can alter plasma concentrations of (BNF 65 2013). One recent meta-analysis (Cipriani et al. 2009) and a later Cochrane review also reported "a trend in favour of sertraline over other antidepressive agents" (Cipriani et al. 2010) although this did not look specifically at the older population.

Whilst the NICE guidance does not suggest a second-line agent if the first proves ineffective, it describes potential issues associated with other antidepressants – for example, the risk of agranulocytosis with mianserin and exacerbation of hypertension with venlafaxine (NICE 2009a). These might incline the practitioner towards mirtazapine as a second-line agent in the older population. Nonetheless there are a number of issues particular to the elderly population which ought to be considered when faced with a choice between the two drugs.

Pharmacokinetics

Polypharmacy can be a significant problem in elderly and thus the pharmacokinetics of these antidepressants is of relevance. Sertraline is metabolised in the liver by cytochrome P450 (CYP) isoenzymes, in particular CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (Spina et al. 2008). It may thus affect metabolism of other drugs using the same CYP. Of note, the CYP2D6 isoenyzme is also involved in metabolism of tricyclic antidepressants and type IC anti-dysrhythmic drugs and so may affect levels of these. Sertraline has the potential to displace drugs bound to plasma proteins such as warfarin and thus could increase a patient's international normalised ratio (INR) (Muijsers et al. 2002), although mirtazapine can also slightly increase the INR (NICE 2009b). There is some suggestion that sertraline has more potential to produce adverse effects than other SSRIs through inhibiting CYP isoenzymes, although this appears to occur in a dose-dependent fashion (Spina et al. 2008).

Mirtazapine is metabolised by hepatic CYP isoenzymes as well; CYP2D6 and CYP3A4 are again suggested to be amongst the more important of these (Spina et al 2008.). Whilst there is potential for mirtazapine levels to be affected by other drugs which induce these enzymes such as carbamazepine, it is not generally considered to be likely to cause problematic drug interactions in a clinical setting (Anttila & Leinonen 2001).

Onset of antidepressant action is also relevant to pharmacokinetics. Sertraline appears to have a longer plasma clearance time in the elderly and is suggested to take up to 2-3 weeks to reach a steady-state level (Muijsers et al. 2002) whereas for mirtazapine this may be achieved in around 6 days (Antilla & Leinonen 2001). Clinical studies also suggest that the therapeutic effect of mirtazapine is achieved earlier. A meta-analysis of adults with major depression indicated remission was more likely to occur within the first two weeks when treated with mirtazapine compared to an SSRI (Thase et al. 2010). A similar result was found in a study comparing sertraline tablets with the orodispersible tablet form of mirtazapine (Behnke et al. 2003). Of further relevance here is that elderly patients may prefer to take such a formulation, although a liquid form of sertaline is also available (UKMi 2011a), which was not considered in this study.

Hyponatraemia

The NICE guidance highlights a particular risk associated with SSRIs of hyponatraemia (NICE 2009b). However, the Cochrane review comparing sertraline to

other antidepressants did not consider hyponatraemia as one of the outcome measures (Cipriani et al. 2010). One meta-anaylsis of second-generation antidepressants including mirtazapine and sertraline reported that there is insufficient evidence regarding the risk of hyponatraemia with these drugs (Gartlehner et al. 2008). More recently other studies have attempted to investigate this further; one found that SSRIs were associated with a significant decrease in serum sodium level, more so in patients over the age of 60. Patients in the trial treated with mirtazapine did not show such changes (Jung et al. 2011). Thus mirtazapine would appear to be preferable to sertraline in older patients at risk of hyponatraemia.

Cardiovascular Disease

As mentioned above, sertraline is the SSRI recommended for use in patients with a history of myocardial infarction and does not prolong the QT interval as citalopram does. For mirtazapine, although the summary of product characteristics has a caution for use in patients with angina or recent myocardial infarction, it does not appear to have significant adverse effects and is recommended as an alternative drug to sertraline (UKMi 2012a).

Many older patients with cardiovascular disease will regularly take aspirin. Due to the inhibition of the serotonin transporter in platelets by SSRIs and consequently a reduced ability for platelets to initiate thrombus formation, the risk of bleeding in patients prescribed both an SSRI and aspirin is increased (Paton & Ferrier 2005). NICE guidance suggests considering mirtazapine in these circumstances as an alternative, or when switching from an SSRI is not possible, to introduce gastroprotective medication (NICE 2009b). This could exacerbate any pre-existing polypharmacy and also increases the cost of treatment.

Other Considerations

Sedative effects are frequently associated with mirtazapine due to its effects upon histamine receptors (Antilla & Leinonen 2001); these could be undesirable for example by increasing the risk of falls in elderly patients, but alternatively might aid difficulty sleeping.

One meta-analysis examining evidence for risks and benefits of different antidepressants in adults suggested that the main adverse effect of mirtazapine was weight gain, whilst that for sertraline was diarrhoea. Interestingly, the discontinuation rates for these therapies were similar (Gartlehner et al. 2008). Weight-gain associated with mirtazapine could potentially be of benefit in frail elderly patients.

Both drugs are cautioned for use in diabetes mellitus and in patients susceptible to angle-closure glaucoma; mirtazapine has an attached caution in patients with a history of urinary retention (BNF 65 2013). However, evidence linking urinary retention with mirtazapine appears sparse; a PubMed search using the terms “mirtazapine urinary retention” gave 3 results. Of these only one case report suggested it could be a significant side effect; this was in an elderly patient with Parkinson disease and benign prostatic hypertrophy (Oulis et al. 2010).

Although primarily undergoing hepatic metabolism, both sertraline and mirtazapine have metabolites which undergo renal excretion, especially mirtazapine. Consequently when prescribed for patients with renal impairment its dose may require reduction (UKMi 2011b).

Sexual dysfunction is associated with SSRIs including sertraline (Muijsers et al. 2002), but not with mirtazapine (Antilla & Leinonen 2001) which may be relevant for some patients.

One study addressed the phenomenon of restless legs syndrome in patients started on antidepressant medication. They found a significant risk of around 28% for developing or having worsening of symptoms of the condition in patients started on mirtazapine, as compared to around 8% for sertraline (Rottach et al. 2008).

The NICE guidance on depression in people with chronic physical health problems summarises some other potential drug interactions to be aware of. Particularly relevant to the elderly population are that mirtazapine may exacerbate postural hypotension, whilst some SSRIs are suggested to worsen symptoms of Parkinson disease (NCCMH 2010). However, evidence for the latter is mixed and thus SSRIs are still the preferred antidepressant with comorbid Parkinson disease (UKMi 2011c).

Comorbid Depression and Dementia

Initial review of the literature highlighted that depression co-existing with dementia is a common issue amongst elderly patients, with a reported prevalence of greater than 20%. The Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD) trial suggested that although both sertraline and mirtazapine reduced a clinical depression score, they did so no more than placebo. Due to the potential side-effects with taking these drugs they suggested a need to re-consider the role of pharmacotherapy in depression associated with dementia (Bannerjee et al. 2011). However, a follow-up study looking at cost-effectiveness concluded that mirtazapine may have benefits versus placebo or sertraline in terms of reducing unpaid care time and costs – possibly by improving insomnia and anxiety (Romeo 2013 et al.).

Cross-titration from Sertraline to Mirtazapine

Guidance on switching antidepressants from NICE suggests this can be achieved in around one week (NICE 2009a). The UK Medicines Information service suggests “cautious cross-tapering” from an SSRI and mirtazapine. The time period for this should depend

upon the individual patient, for example their starting antidepressant dose and presence of any withdrawal symptoms that occur. but generally could involve reducing the dose of the one drug and increasing that of the replacing antidepressant at one to two week intervals (UKMi 2012b). However, one study suggests that in patients in whom an SSRI has been unsuccessful, patients may be rapidly changed to mirtazapine. From a maintenance dose of an SSRI, patients immediately switched to mirtazapine had no greater risk of adverse events than those who had a placebo for 4 days prior to switching (Hirschfeld 2002).

CONCLUSION

Sertraline and mirtazapine are both suitable choices of antidepressant in the older patient. In certain situations one may be preferable over the other.

Mirtazapine appears to have less prospensity for drug interactions and gives more rapid clinical improvement. Its orexigenic effects may help promote weight gain in frail elderly individuals and the drug is not associated with sexual dysfunction. Furthermore it does not appear to be as associated with hyponatraemia as the SSRIs, whilst its sedating action has been suggested to improve sleep, which may in turn have beneficial impacts upon carer burdens (for those with comorbid depression and dementia). Arguably however this might also increase a patient's falls risk.

Sertaline is preferable in patients with renal impairment due to the extensive renal clearance of metabolites of mirtazapine. It is more suitable in patients taking antihypertensives due to exacerbation of postural hypotension with mirtazapine and is less strongly associated with restless legs syndrome. However, use of sertraline may increase risk of gastrointestinal bleeding, especially if a patient is on aspirin, either limiting its use or necessitating concomitant prescription of a gastroprotective agent.

Whilst mirtazapine is only indicated for use in major depression, contrasting with sertraline which is also licensed anxiety and obsessive-compulsive disorders (BNF 65 2013), clinical studies indicate that mirtazapine may be useful in these as well (Croom et al. 2009).

Because of the co-morbidities associated with older age, mirtazapine would appear to have advantages over sertraline for some patients in the treatment of depression. There does not appear to be evidence to strongly favour one drug over the other. Cross-titration can be performed with caution using clinical judgement if a switch is desired.

Interestingly one observational study suggested that SSRIs and mirtazapine may both be linked with increased all-cause mortality compared to tricyclic antidepressants in patients over the age of 65. Mirtazapine in particular was associated with attempted self-harm and stroke. However, as the authors of the report admit, there were many confounding factors in their analysis (Coupland et al. 2011).

Nonetheless, sometimes it may be inappropriate to continue use of antidepressants. The results of the observational study above also identified an increased risk of all-cause mortality for all classes of antidepressant drug considered (Coupland et al. 2011). Although two Cochrane reviews (Mottram et al. 2006, Wilson et al. 2001) conclude antidepressants to be effective in the elderly, the result of the HTA-SADD trial (Banerjee et al. 2011) and another meta-analysis suggesting these drugs to be less efficacious in people over the age of 65 years (Tedeschini et al. 2011), stress the importance of taking a bio-psycho-social (Blazer 2009) approach towards geriatric depression.

Acknowledgements: None.

Conflict of interest:

This article is based on a presentation given to the Department of Medicine for the Elderly at Addenbrook's Hospital in May 2013.

References

1. *Alexopoulos GS & Kelly, Jr. RE: Research Advances in Geriatric Depression. World Psychiatry 2009; 8:140-149.*
2. *Anttila SAK & Leinonen EVJ: A Review of the Pharmacological and Clinical Profile of Mirtazapine. CNS Drug Reviews 2001; 7:249-264*
3. *Banerjee S, Hellier J, Dewey M, Romeo R, Ballard C, Baldwin R et al.: Sertraline or mirtazepine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. Lancet 2011; 378:403-411.*
4. *Behnke K, Søgaard J, Martin S, Bäuml J, Ravindran AV, Agren H et al.: Mirtazapine orally disintegrating tablet versus sertraline: a prospective onset of action study. J Clin Psychopharmacol 2003; 23:358-364.*
5. *Blazer DG: Depression in Late Life: Review and Commentary. Focus 2009; 7:118-136.*
6. *British Medical Association & the Royal Pharmaceutical Society of Great Britain: British National Formulary (BNF) 65. BMJ Publishing Group and Pharmaceutical Press, London, 2013.*
7. *Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JPT, Churchill R et al.: Comparative Efficacy and Acceptability of 12 New-Generation Antidepressants: a multiple-treatments meta analysis. Lancet 2009; 373:746-758.*
8. *Cipriani A, La Ferla T, Furukawa TA, Signoretti A, Nakagawa A, Churchil R et al.: Sertraline versus other antidepressive agents for depression. Cochrane Database of Systematic Reviews 2010; Issue 4.*
9. *Coupland C, Dhiman P, Morriss R, Arthur A, Barton G & Hippisley-Cox J: Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 2011; 343:d4551.*
10. *Croom KF, Perry CM & Plosker GL: Mirtazapine: a review of its use in major depression and other psychiatric disorders. CNS Drugs 2009; 23:427-452.*
11. *Gallo JJ, Morales KH, Bogner HR, Raue PJ, Zee J, Bruce ML et al: Long term effect of depression care management*

on mortality in older adults: follow-up of cluster randomized clinical trial in primary care. BMJ 2013; 346:f2570.

12. *Gartlehner G, Gaynes BN, Hansen RA, Thieda P, DeVeaugh-Geiss A, Krebs EE et al.: Comparative Benefits and Harms of Second-Generation Antidepressants: Background Paper for the American College of Physicians. Ann Intern Med 2008; 149:734-750.*
13. *Hirschfeld RA: The use of mirtazapine in difficult-to-treat patient populations. Hum Psychopharmacol Clin Exp 2002; 17:S33-S36.*
14. *Jung YE, Jun TY, Kim KS & Bahk WM: Hyponatraemia Associated with Selective Serotonin Reuptake Inhibitors, Mirtazapine, and Venlafaxine in Korean Patients with Major Depressive Disorder. Int J Clin Pharmacol Ther 2011; 49:437-443.*
15. *Mottram PG, Wilson K & Strobl JJ: Antidepressants for depressed elderly. Cochrane Database of Systematic Reviews 2006; Issue 1.*
16. *Muijsers RBR, Plosker G & Noble S: Sertraline: A Review of its Use in the Management of Major Depressive Disorder in Elderly Patients. Drugs & Aging 2002; 19:377-392.*
17. *NCCMH: Depression in Adults with a Chronic Physical Health Problem. British Psychological Society and the Royal College of Psychiatrists, Leicester & London, 2010.*
18. *NICE: Depression: The Treatment and Management of Depression in Adults (update). Clinical Guideline 90. NICE, London, 2009. (a)*
19. *NICE: Depression in Children and Young People: Identification in Primary, Community and Secondary Care. Clinical Guideline 28. NICE, London, 2005.*
20. *NICE: Depression in Adults with a Chronic Physical Health Problem: Treatment and Management. Clinical Guideline 91. NICE, London, 2009. (b)*
21. *Oulis P, Leonardos A, Koulouris GC & Konstantakopoulos G: Mirtazapine-Associated Urinary Retention. J Neuropsychiatry Clin Neurosci 2010; 22:352.E21-352.E22.*
22. *Paton C & Ferrier IN: SSRIs and Gastrointestinal Bleeding: Gastroprotection may be Justified in Some Patients. BMJ 2005; 351:529-530.*
23. *Romeo R, Knapp M, Hellier J, Dewey M, Ballard C, Baldwin R et al.: Cost-effectiveness analyses for mirtazepine and sertraline in dementia: randomised control trial. Br J Psych 2013; 202:121-128.*
24. *Rottach KG, Schaner BM, Kirch MH, Zivotofsky AZ, Teufel LM, Gallwitz T et al.: Restless Legs Syndrome as Side Effect of Second Generation Antidepressants. J Psychiatr Res 2008; 43:70-75.*
25. *Schulz R, Drayer RA & Rollman BL: Depression as a Risk Factor for Non-Suicide Mortality in the Elderly. Biol Psychiatry 2002; 52:205-225.*
26. *Spina E, Santoro V & D'Arrigo C: Clinically Relevant Pharmacokinetic Drug Interactions with Second-Generation Antidepressants: An Update. Clinical Therapeutics 2008; 30:1206-1227.*
27. *Tedeschini E, Levkovitz Y, Iovieno N, Ameral VE, Nelson JC & Papakostas GI: Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials. J Clin Psychiatry 2011; 72:1660-1668.*
28. *Thase ME, Nierenberg AA, Vrijland P, van Oers HJ, Schutte AJ & Simmons JH: Remission with mirtazapine and selective serotonin reuptake inhibitors: a meta-analysis of individual patient data from 15 controlled trials of acute phase treatment of major depression. Int Clin Psychopharmacol 2010; 25:189-198.*
29. *UKMi: What is the antidepressant of choice in coronary heart disease? (monograph on the internet). London Medicines Information Service 2012 (cited 2013 Jul 17). Available from http://www.medicinesresources.nhs.uk/upload/NHSE_What_is_the_antidepressant_of_choice_in_coronary_heart_disease_final%5B1%5D.docx. (a)*
30. *UKMi: Therapeutic options for patients unable to take solid oral dosage forms (monograph on the internet). North West Medicines Information Centre 2011 (cited 2013 Jul 17). Available from http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Medicines%20Q%20&%20A/NW%20QA294.2%20Therapeutic%20options%20for%20patients%20unable%20to%20take%20solid%20oral%20dosage%20forms.doc. (a)*
31. *UKMi: What is the first choice antidepressant for patients with renal impairment? (monograph on the internet). South West Medicines Information and Training 2011 (cited 2013 Jul 17). Available from http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Medicines%20Q%20&%20A/QA369-Antidepressants-in-RI-jan11-FINAL-rev.doc. (b)*
32. *UKMi: How should depression be treated in a patient with Parkinson's disease? (monograph on the internet). West Midlands Medicines Information Service 2011 (cited 2013 Jul 17). Available from http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Medicines%20Q%20&%20A/QA71-3_DepressionPD_final.doc. (c)*
33. *UKMi: Switching between tricyclic, SSRI and related antidepressants (monograph on the internet). North West Medicines Information Centre 2012 (cited 2013 Jul 17). Available from http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Medicines%20Q%20&%20A/NW%20QA150.4%20switching%20antidepressants%20-%20SSRIs,%20TCAs%20and%20related.doc. (b)*
34. *Wilson K, Mottram PG, Sivanthan A & Nightingale A: Antidepressants Versus Placebo for the Depressed Elderly. Cochrane Database of Systematic Reviews 2001; Issue 1.*

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