Guideline Supplementary Paper

New Zealand Autism Spectrum Disorder Guideline
supplementary paper on three pharmacological interventions

New Zealand GUIDELINES GROUP
Te Rōpū Rarangi Tohutohu
Promoting Effective Health and Disability Services

With the support of the New Zealand Autism Spectrum Disorder
Living Guideline Group

March 2011

Published by: New Zealand Guidelines Group
PO Box 10 665, The Terrace
Wellington, New Zealand

ISBN (electronic): 978-1-877509-53-7

Suggested citation
Marita Broadstock. New Zealand Autism Spectrum Disorder guideline supplementary paper on three pharmacological interventions. Wellington: New Zealand Guidelines Group; 2011.

Access to document
This publication is available at www.nzgg.org.nz – search on publication title.

HP5439

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Supplementary Paper on Three Pharmacological Interventions for the New Zealand Autism Spectrum Disorder Guideline

1. Background

1.1 Preamble

The Ministry of Health and Ministry of Education ('the Ministries') jointly funded the development of a New Zealand Autism Spectrum Disorder Guideline (NZ ASD Guideline) which was released in April 2008.[1]

A living guideline process was set up to keep the NZ ASD Guideline current, and a Living Guideline Group (LGG) was convened by the New Zealand Guidelines Group (NZGG) to carry out this process. The goal of the LGG is to ensure that the recommendations in the NZ ASD Guideline remain up-to-date and relevant as evidence changes. It focuses on areas where new evidence has emerged that may warrant a re-examination or change in a NZ ASD Guideline recommendation. The LGG membership is presented in Appendix A.

The first topic considered by the LGG was Applied Behaviour Analysis (ABA)[1]. The second topic, dealt with in the current report, considers evidence relating to three pharmacological interventions for people with ASD.

1.2 Pharmacological interventions in ASD

While educational and behavioural treatments continue to form the primary treatment method for people with autism spectrum disorder, the use of pharmacotherapy is being used increasingly as an adjunctive treatment or when psychological interventions have proven ineffective. Although pharmacological agents will not cure ASD, they may help manage specific physical, behavioural or psychiatric conditions associated or comorbid with autism.[2]

Although the effectiveness and safety of pharmacological agents for people with ASD is a burgeoning area of research, there has also been a rapid increase in the clinical use of pharmacotherapy. ASD can be associated with substantial impairment and people with ASD and/or their caregivers can be particularly vulnerable to trying pharmacological treatments without solid supporting evidence. It is therefore crucial that clinicians provide

[1] http://www.health.govt.nz/our-work/disability-services/disability-projects-and-programmes/autism-spectrum-disorder-guideline/keeping-guideline-date

consumers with clear information about the limits of the evidence available, the potential for side effects and adverse events, and alternatives open to them.

1.3 The Living Guideline Group process

Pharmacotherapies are discussed in Section 4.4 of the NZ ASD Guideline. Three medications were identified by the LGG as having evidence published in recent years which may impact on the currency of existing ASD Guideline recommendations for their use. These interventions are: the atypical antipsychotic **aripiprazole** (also sold internationally as *Abilify*, and *Abilify Discmelt*), the selective serotonin reuptake inhibitor (SSRI) **citalopram** (sold under the brand-names *Celexa, Arrow Citalopram, Celapram, Citalopram-Rex* and *Cipramil*), and the hormone, **melatonin**.

A systematic review was conducted by the New Zealand Guidelines Group (NZGG)[2] to update evidence from the NZ ASD Guideline on these three pharmacological agents. The review update critically appraised evidence on the three pharmacological interventions published from January 1st 2004. Any controlled study assessing effectiveness was eligible for inclusion, as well as systematic reviews of the interventions. Despite the NZ ASD Guideline being developed for all people with ASD, the original search strategy was aimed at identifying evidence on the benefits and harms of pharmacological and biomedical interventions suitable for children with ASD, aged 0 to 12 years. However, no age limit was placed on the samples included in the current review update

The review update was considered by the LGG at a face-to-face meeting held in November 2010. The evidence base was discussed in terms of its impact on the wording and evidence grading of current recommendations in the NZ ASD Guideline of potential relevance. The development of new recommendations was also considered. Revised and new recommendations were graded using the NZGG Grading System, also used for the NZ ASD Guideline, detailed in Appendix B. Grading decisions are made on the quality, quantity, consistency, applicability and clinical impact of all the studies forming the relevant body of evidence. Assessment of the updated evidence relevant to the three pharmacological interventions resulted in a number of revised or modified recommendations from the NZ ASD Guideline as well as newly developed recommendations. This supplementary paper reports these decisions and summarises the evidence from the systematic review update that was drawn on by the LGG in its deliberations.

[2] Broadstock, M. A systematic review of three pharmacological interventions for the New Zealand Autism Spectrum Disorder Living Guideline Group. Wellington, NZ: New Zealand Guidelines Group; 2010. Available from: http://www.insightresearchltd.com/living-guideline-group.html

2. Aripiprazole

2.1 Context

Of pharmacological interventions used for people with ASD, antipsychotic medications have been the most critically investigated. Target symptoms of treatment for people with ASD using antipsychotics can include irritability, aggression, self-injurious behaviour, and severe tantrums.[3] The clinical definition of irritability is beyond and different to the everyday meaning of 'being irritable'. As measured by the Aberrant Behaviour Checklist – Irritability (ABC-I) scale, it can be exhibited as temper tantrums, yelling, crying, stamping feet, mood changes, and physical violence. Irritability is often accompanied by aggression directed toward self and others. Aggression can often be impulsive in nature and can result in significant physical injury toward others or destruction of property. By comparison, the self-injurious behaviour can have a repetitive or compulsive quality and at times can result in severe damage (eg, retinal detachment, subdural haematoma).[4] Clearly, irritability in all its forms can pose substantial challenges to the affected individual and those around them, and therefore interventions to effectively manage aggression, self-injurious behaviour, and severe tantrums have been eagerly sought.

Second-generation, *atypical antipsychotic* agents (eg, clozapine, olanzapine, risperidone, quetiapine) have been associated with metabolic and endocrine adverse effects, particularly in children.[5] Significant weight gain in children with autism has been associated with both short- and long-term administration of atypical antipsychotics, which can continue for weeks or months.[6] Sedation is also frequently associated with use of antipsychotics, particularly in the early weeks of treatment.

In the ASD Guideline,[1] risperidone is the only medication in this class to be explicitly endorsed for specific indications (Recommendation 4.4.3). It is said to be 'effective in reducing aggressive behaviour, irritability and self-injurious behaviour in children with ASD', and 'may be useful in improving restricted interests and patterns of behaviour'. With respect to alternatives within this class of drugs, the guideline currently suggests that 'there is insufficient evidence to make any specific recommendation regarding atypical antipsychotic agents other than risperidone', adding, 'clinicians prescribing these drugs need to keep up to date with current literature' (Recommendation 4.4.4). Supporting this recommendation, it is noted in the text that 'a number of other atypical antipsychotic medications exist, although no RCTs relating to their use in ASD have been found by the Guideline Development Team'

The atypical antipsychotic aripiprazole has been proposed for the treatment of irritability as an alternative to risperidone because of its potential for having a better side effect profile. Possible advantages of aripiprazole over other available atypical antipsychotics have been suggested, including that aripiprazole does not appear to impact on cardiac function, and that it appears to have a lesser impact on metabolic parameters, with

reduced impact on weight or body mass index, and less significant changes in glucose, lipid metabolism and serum prolactin.[7]

There is currently no mention of aripiprazole in the ASD Guideline. Currently in New Zealand, aripiprazole is only funded for adult psychotic disorders and requires a Special Authority approval using form SA0920 (http://www.pharmac.govt.nz/?q=aripiprazole). This approval can be sought by any relevant medical practitioner, and requires risperidone or quetiapine to have been trialled and discontinued due to inadequate clinical response or unacceptable side effects.

2.2 Body of evidence

Eight studies were critically appraised in the review update: six systematic reviews [6-11] and two randomised controlled trials.[12, 13] The quality of appraised reviews was generally not high, with three being rated using the formal checklist as of poor quality, two as variable, and only one study as of good quality.[11] The reviews identified a total of six uncontrolled open label studies and interim or full data from two multi-centre randomised controlled trials, both of which were of high quality.

2.3 Summary of findings

Two well conducted randomised controlled studies (RCTs)[12, 13] involving young people aged 6-17 years with ASD suggest promising, emerging evidence that aripiprazole, particularly when used in a clinical situation where dose-adjustment is permitted, can have beneficial effects on irritability, global improvement, and quality of life. Moreover, they suggest that the drug is generally well tolerated, with relatively small weight gains (1.3-1.5kg) observed over a two month follow-up period.

The findings of the two RCTs are broadly consistent with the conclusions of the six appraised systematic reviews. However the LGG note that the evidence base for efficacy and safety is small, with only two, similarly designed controlled trials with a common study setting and similar population, and a handful of small, open label studies, all with short follow-up periods.

2.4 Recommendation development

The LGG discussed the relative advantage of aripiprazole over risperidone in terms of its side effect profile, especially with respect to weight gain. It was agreed that aripiprazole may be a potentially effective alternative to the first line atypical antipsychotic risperidone where this medication has not been effective or where significant metabolic or adverse effects have arisen, or are likely to arise. However it was noted that there has been no comparative or head-to-head study of aripiprazole with risperidone or other agents from its class.

Whilst the mechanism of action of aripiprazole is unclear, it was acknowledged that this is also the case for other antipsychotics.

The LGG agreed that the evidence suggests a cautious approach to the use of aripiprazole at the present time. For those most vulnerable to side effects including children, and particularly in the treatment of irritability and aggression in people with PDD, lower initial and target doses are advisable. Ongoing monitoring of metabolic parameters is also recommended, incuding weight or body mass index, pulse, blood pressure, glucose and lipid metabolism, and possibly serum prolactin.

As the possibility of aripiprazole causing tardive dyskinesia cannot be excluded, baseline and periodic testing using the Abnormal Involuntary Movements Scale (AIMS) was highlighted. The LGG noted that aripiprazole should be initiated within the care of secondary care clinicians.

The LGG advise that careful consideration, informed consent and ongoing monitoring is necessary before this medication is considered as a first-line treatment in people with ASD.

2.5 Revised and modified recommendation

Original recommendation	Grade
4.4.4 There is insufficient evidence to make any specific recommendation regarding atypical antipsychotic agents other than risperidone. Clinicians prescribing these drugs need to keep up to date with current literature.	**I**
Revised recommendation	**Grade**
4.4.4 In most circumstances risperidone should be the first medication used when indicated for significant irritability in children and young people with ASD. Aripiprazole could be used as a second-line treatment where individuals have demonstrated poor efficacy to risperidone or where there is concern regarding significant metabolic or adverse effects. Clinicians prescribing these drugs need to keep up to date with current literature.	**B**

3. Citalopram

3.1 Context

SSRIs have been used to treat obsessive-compulsive disorder (OCD). Possible similarities between the repetitive behaviours seen in OCD and ASD have led to the consideration of SSRIs in treating repetitive behaviour in people with ASD. Repetitive behaviour can be a disruptive and troubling feature of ASD, and may involve stereotypic movements, inflexible routines, repetitive play, and perseverative speech. Interrupting such routines can lead to anxiety, protest, aggression, and self-injury.

The SSRIs most commonly prescribed in New Zealand for children are fluoxetine and citalopram.[14] The ASD guideline[1] does not refer to citalopram explicitly in the main body of the report, however it advises (in Recommendation 4.4.1) that SSRIs generally 'may be effective for some children with ASD and high anxiety and/or obsessive symptoms'. The recommendation continues, 'however, in the absence of good evidence, these drugs should be used with caution and careful monitoring'. Citalopram is included in Appendix 9 of the ASD Guideline (Table 9.1) as an SSRI used in NZ for people with ASD. The table notes that citalopram is 'more selective, therefore (with) fewer adverse events'.

In New Zealand, citalopram is subsidised and may be used 'off label'. This is common for medications used in children and adolescents, and means the medication is licensed by the regulatory authority for use in adults or only for restricted indications, even when research evidence points to use for broader indications or age ranges.

3.2 Body of evidence

The review update identified preliminary open-label trials of the use of citalopram, for people with ASD,[15, 16] two good quality systematic reviews,[2, 11] and a high quality multi-centre, triple blinded study[17] of 149 children and adolescents, potentially the largest randomised medication trial ever conducted in children with ASD.[18]

3.3 Summary of findings

Results suggest that citalopram is not effective in treating children and young people with ASD with moderate or greater repetitive behaviour, and is associated with a small increase in mild to moderately severe adverse events. The most common of these were: increased energy level, impulsiveness, decreased concentration, hyperactivity, stereotypy, diarrhoea, insomnia, and dry skin or pruritus.

The key primary evidence comes from a single study,[17] however it is of a relatively large size for autism research, is multi-centre, and is a randomised controlled trial appraised

as being of high quality. Interpretation of this large, well conducted RCT was consistent with that of a systematic review[2] included in the review update.

3.4 Recommendation development

The LGG recognise that repetitive behaviours are not always a concern for a person with ASD, and that it is important to determine the interference of the behaviour with daily functioning, harm to self and others, and distress, when assessing the need for intervention.

Whether there may be a class effect generally with SSRIs was discussed in view of conclusions of a recently published Cochrane review,[2] however as the current systematic review focused on the role of citalopram alone, this was outside the scope of the LGG's guidance.

The LGG concluded that the balance of evidence for benefit and harm at a clinical level was such that citalopram could not be currently recommended for the pharmacological treatment of repetitive behaviour in children and young people with ASD. Caution was also urged in its use for established comorbid indications in this population given the evidence of adverse events.

It should be noted that the study sample upon which the new recommendations were developed were children and adolescents. Whilst the review update was not restricted in its scope to younger people, unfortunately there is a lack of new research in adult populations. Caution is necessary in translating results from one age/developmental group to another, hence the specification of children and young people in the new recommendations relating to citalopram.

3.5 New recommendations

New recommendation	Grade
4.4.1a. Citalopram cannot currently be recommended for the treatment of repetitive behaviours in children and young people with ASD.	**B**

New recommendation	Grade
4.4.1b. Citalopram's use for established comorbid indications for children and young people (eg, anxiety, obsessive compulsive disorder) should be considered with significant caution on a case-by-case basis, after full disclosure of side effects to the individual and their family and careful ongoing monitoring.	**C**

4. Melatonin

4.1 Context

Sleep difficulties are common in people with ASD, with abnormal sleep patterns reported in up to 89% of children with ASD.[19] Dyssomnias (ie, difficulty falling asleep and frequent night-time awakenings) are the most commonly reported sleep problems.[20] Where behavioural treatment is ineffective, sedatives can be prescribed, however these may induce serious side effects such as daytime sedation, increased risk of sleep related breathing problems and behavioural problems.

The reason why sleep problems are so common in children with ASD is not clear, but one suggested explanation relates to reports of abnormal melatonin synthesis in people with ASD[21] and abnormal melatonin levels in children with ASD.[20] Melatonin is a hormone produced in the human brain, secreted mainly from the pineal gland, which regulates the sleep–wake cycle, the circadian rhythm. Melatonin is synthesised from serotonin in a diurnal pattern with blood-level rising around 21:00 hours and remaining elevated for 12 hours before receding to a trough during the daytime.[22] It is possible that inappropriately timed or deficient melatonin secretion may be associated with persistent nightly sleep onset delay and prolonged awakenings.[23]

The body's melatonin can be supplemented by ingesting products containing melatonin. It has been hypothesised that supplementation of melatonin selectively benefits those sleep disorders associated with an underlying nocturnal melatonin deficit, such as has been found in children with ASD.[23]

The ASD Guideline[1] includes the following recommendation regarding melatonin: 'melatonin may be useful for improving sleep in children with ASD who have impaired sleep' (Recommendation 4.4.7). This recommendation is graded B (representing 'fair evidence'). Further, the Guideline advises that caution is needed for using melatonin as formulations may vary and the appropriate dose is not clear.[1]

Currently products containing melatonin are neither registered for use as a sleep aid nor funded in New Zealand but can be purchased in various formulations from retail pharmacies upon presentation of a prescription.[1] In the UK melatonin is also considered a medicinal product and is yet to be licensed.[22] By contrast, in the USA melatonin is the only hormone available without a prescription. It is available as a food supplement across a range of orally administered doses in tablets, capsules, sublingual lozenges, and liquid forms.

4.2 Body of evidence

The review update appraised four systematic reviews,[11, 22, 24, 25] and one cross-over trial.[23] Review quality varied, with two rated as good and two as being of poor quality. The reviews identified eight primary studies evaluating melatonin explicitly: two large retrospective studies; three open label studies; and three crossover RCTs. One trial of good quality was eligible for appraisal; a cross-over trial of 51 children and adolescents with multiple neurodevelopmental disabilities and treatment resistant sleep problems, 16 of whom had ASD.

4.3 Summary of findings

There is good and consistent evidence that melatonin is beneficial in treating persistent sleep problems for people with ASD to a moderate but clinically significant degree, particularly where professionally designed behavioural strategies have failed. Specifically, melatonin's benefits included decreasing sleep latency (ie, reducing time before sleep onset), decreasing the number of wakes per night, and increasing total sleep time.

With respect to safety, studies uniformly have found side effects during melatonin treatment to be minor and infrequent, and in controlled studies, at similar frequencies as for those receiving placebo.

The conclusions of the four appraised reviews were largely consistent despite variations in the included primary studies, and the fact that some reviews considered many studies from non-ASD populations. These results were supported by the findings of the good quality, blinded cross-over trial[23] appraised in the review update.

It was noted that melatonin is an area of active research interest. A double-blind, parallel group multi-centre RCT evaluating melatonin (the MENDS trial) (http://pfsearch.ukcrn.org.uk/StudyDetail.aspx?TopicID=4&StudyID=2258) has recruited approximately 160 children (aged 3-15 years) with 'developmental delay', some of whom have ASD. Data at 12-week follow-up has been collected and the report is expected to be published by the project's funder, the UK's National Institute for Health Research (NIHR), in May/June 2011. The LGG has undertaken to consider the results of this trial once available in terms of whether they warrant revisions to relevant recommendations and/or their grade.

4.4 Recommendation development

The LGG agreed that Recommendation 4.4.7 should be strengthened in view of the updated evidence.

It was noted that level of impairment to quality of life as a function of sleep problems, for the individual and their family, is important to consider in deciding whether to use melatonin.

There is as yet no consensus on the therapeutic dose of melatonin for children and adolescents. The studies cited have generally used a 5mg dose, however the LGG suggested that in clinical practice it is appropriate and useful to initiate with lower doses, of 1 or 2 mg. There was a suggestion that controlled release melatonin is not always practical for children with ASD, as many children with ASD are not able to swallow tablets or capsules whole, but it may have advantages over fast-release formulations for those children who have trouble sustaining sleep.

The LGG note that the evidence has a number of limitations. The number of controlled trials is few. There are no long-term investigations of melatonin, with the longest follow-up in controlled studies being one month. In one small open-label study[26] extending over 2 years, improved sleep appeared to be maintained at 12 and 24 month follow-up but sleep problems returned for 16 of 25 children when melatonin was discontinued. Such findings suggest that sleep difficulties can be a chronic problem requiring ongoing treatment. The benefits and side effects of longer-term treatment require further investigation under controlled conditions. This need is captured in the development of a new research Recommendation. As for citalopram, the evidence base is predominantly derived from children and young people and its applicability to adults is uncertain.

Given these uncertainties, the LGG recommended caution in the administration of melatonin over the longer term, and that behavioural strategies including improvements to sleep hygiene should also be attempted in parallel with melatonin. Sleep hygiene is the regulation of daily activities and environmental factors aimed at maintaining good quality sleep and daytime alertness. Strategies might include having a quiet bedroom, employing a regular sleep time schedule, and the avoidance of stimulants and late night recreations.

4.5 Revised and modified recommendation

Original recommendation	Grade
4.4.7 Melatonin may be useful for improving sleep in children with ASD who have impaired sleep.	**B**
Revised recommendation	**Grade**
4.4.7 Melatonin can be recommended for use in children and young people with ASD who are experiencing significant sleep problems**.**	**B**

4.6 New recommendations

New recommendation	Grade
Benefits and adverse effects of longer term treatment of melatonin require further investigation**.**	**C**

New recommendation	Grade
Behavioural strategies (eg, sleep hygiene) should always be used in conjunction with melatonin.	**C**

5. Important Note to Prescribers

The NZ ASD Guideline included an ‘Important note for prescribers’ which is also relevant to the three pharmacological interventions and to this supplementary report. Passages are reproduced here for reference.

> As prescribing information may change during the course of this guideline, the guideline group has deliberately not provided full information about the status of medications in relation to registration, funding and manufacturer's recommendations.
>
> All prescribers must ensure that they are informed of current information in relation to medications that they use and they should be aware when they are using medications that are ‘off-label’. All medications should be used with caution and patients should be carefully monitored while taking medication. Clinicians are expected to prescribe safely and should be knowledgeable about potential interactions. In particular, prescribers need to keep up to date with current literature, especially in relation to newly reported adverse effects and 'black box' warnings.

Acknowledgements

This report is based on the work of the Living Guideline Group (LGG), a multidisciplinary team convened by the New Zealand Guidelines Group and funded by the New Zealand Ministries of Health and Education. At this meeting the Living Guideline Group was chaired by **Matt Frost** with **Dr Matt Eggleston** as Deputy Chair. Full membership and affiliations are listed in Appendix A.

Ex-officio LGG members include **Dr Elizabeth Doell** (Ministry of Education) and **Leigh Sturgis** (Ministry of Health).

Marita Broadstock (NZGG Senior Researcher) is the LGG Project Manager and assisted the LGG in drafting this report based on its deliberations.

Thanks also to NZGG staff including **Dr Jessica Berentson-Shaw** and **Stuart McCaw** for project development and terms of reference, and to **Stephanie Dixon** and **Paula Bell** for assistance in providing administrative support to the LGG.

Appendix A

Membership of Living Guideline Group (as at December 2010)

Professor Ian Evans (Chair, on leave of absence from LGG July-December 2010), School of Psychology, Massey University.

Matt Frost (Acting Chair), Autism New Zealand.

Associate Professor Jill Bevan-Brown, Director, Inclusive Education Research Centre, College of Education, Massey University.

Dr Sally Clendon, Senior Lecturer, Speech Language Therapy Programme, School of Education at Albany, College of Education, Massey University.

Dr Matt Eggleston (Deputy Chair) Child and Adolescent Psychiatrist, Clinical Head, Child and Family Specialty Service, Canterbury DHB.

Dr Debbie Fewtrell, General Practitioner (special interest in autism spectrum disorder), Kerikeri.

Dr Andrew Marshall, Developmental Paediatrician, Child Development Team at Puketiro Centre, Porirua.

Ex-officio LGG members:

Dr Elizabeth Doell, Practice Leader, Communication, Special Education, Southern Regional Office, Ministry of Education

Leigh Sturgiss, ASD Project Manager, Family and Community, Disability Support Services, National Services Purchasing, National Health Board, Ministry of Health.

Appendix B

Evidence grading system.[1]

Grade	Meaning of Grade
A	The recommendation is supported by GOOD evidence (where there is a number of studies that are valid, applicable and clinically relevant)
B	The recommendation is supported by FAIR evidence (based on studies that are mostly valid, but there are some concerns about the volume, consistency, applicability and/or clinical relevance of the evidence that may cause some uncertainty, but are not likely to be overturned by other evidence).
C	The recommendation is supported by EXPERT OPINION only (from external opinion, published or unpublished, eg, consensus guidelines).
I	No recommendation can be made. The evidence is insufficient (either lacking, of poor quality or conflicting, and the balance of benefits and harms cannot be determined).

Good Practice Point

✓	Where a recommendation is based on the clinical and educational experiences of members of the guideline development teams, this is referred to as a good practice point.

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