Psychopharmacology

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Abbreviations

ABC	Aberrant Behaviour Checklist
ADHD	Attention Deficit Hyperactivity Disorder
ASD	Autistic Spectrum Disorder
BPI	Behavior Problems Inventory
CGI	Clinical Global Impressions Scale
DASH	Diagnostic Assessment for the Severely Handicapped
DISCUS	Dyskinesia Identification System
DOTES	Dosage Record and Treatment Emergent Symptom Scale
ECG	Electroencephalograph
ESRS	Extrapyramidal Symptoms Rating Scale
ID	Intellectual disabilities
ITT	Intention to treat
MOAS	Modified Overt Aggression Scale
NCBR-F	Nisonger Child Behavior Rating Form
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
OCD	Obsessive Compulsive Disorder
ONE	Objective Neurological Examination
PIMRA	Psychopathology Instrument for Mentally Retarded Adults
RCT	Randomised controlled trial
RUPP	Research Unit of Pediatric Psychopharmacology
SIB	Self-injurious behaviour
SOME	Summation of Maladaptive Expression
SSRIs	Selective serotonin reuptake inhibitors
VAS	Visual Analogue Scale

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Introduction

It has been reported that 20–50 % of people with intellectual disabilities (ID) receive psychotropic medications (Deb & Unwin, 2007a). It has been reported that 36 % of those who receive psychotropic medications do not have a psychiatric diagnosis (Clarke, Kelley, Thinn, & Corbett, 1990). People with ID often receive multiple medications and often at a high dose (Deb & Fraser, 1994). In a recent prospective 12-month follow-up study of 100 adults who have been seen by psychiatrists in the UK in their outpatient clinics for the management of aggressive behaviour, Unwin, Rashid, and Deb (2011) found more than 90 % of the participants received psychotropic medications. Of them 66 % received antipsychotics, 42 % antiepileptic, 35 % antidepressants, 14 % antianxiety/beta blockers, and

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43 % as required medications, and 23 % received medications to counteract adverse effects of other psychotropic medications. In a consensus study among psychiatrists in the UK on the use of medication for the management of aggression and self-injurious behaviour (SIB), Unwin and Deb (2008) found that most psychiatrists preferred to use a non-medication-based management first. However, if they had to use a psychotropic medication, the order of preference was usually an antipsychotic followed by an antidepressant followed by a mood stabiliser. Among the antipsychotics, the newer antipsychotics were preferred in the order of risperidone followed by olanzapine, quetiapine, amisulpride, aripiprazole and clozapine. Among the antidepressants, the order of preference was citalopram followed by fluoxetine, sertraline, escitalopram, mirtazapine, paroxetine, venlafaxine and fluvoxamine. Psychiatrists usually considered psychotropic medications under the following circumstances: (a) failure of non-medication-based interventions; (b) risk/evidence of harm to others, property and self; (c) high frequency and severity of problem behaviours; (d) to treat an underlying psychiatric disorder or anxiety; (e) to help with the implementation of non-medication-based interventions; (f) risk of breakdown of the person's community placement; (g) lack of adequate or available non-medication-based interventions (although this should not be used as a rationale for using medication); (h) good response to medication in the past; and (i) patient/carer choice.

The main concerns for using psychotropic medications in the absence of a diagnosed psychiatric disorder are that these medications in general are not licensed for the management of problem behaviour without a psychiatric diagnosis; there is potential for adverse effects particularly if these medications are used for a long time, yet it is difficult to withdraw these medications once started because of the potential withdrawal symptoms and resurgence of problem behaviour and the lack of evidence for the effectiveness of psychotropic medications in the absence of a psychiatric diagnosis. Therefore, systematic reviews have been carried out on the effectiveness of different types of psychotropic medications which have been summarised in this chapter. The evidence base for the effectiveness of different psychotropic medications for different types of psychiatric disorders such as schizophrenia, depressive disorders and anxiety disorders is summarised in the respective National Institute for Health and Clinical Excellence (NICE) guidelines in the UK (www.nice.org.uk) and in similar guidelines in other countries. These guidelines should be used for people with ID with different psychiatric disorders in the absence of any specific guidelines for these people. Therefore, in this chapter the evidence for the use of different psychotropic medications for people with ID only for the management of problem behaviour in the absence of any psychiatric disorder is summarised. This chapter concentrates primarily on studies on adults, although for antipsychotics data from children's studies as well have also been presented.

These systematic reviews were carried out in order to develop a national and an international guide for the management of problem behaviour in people with ID (Deb et al., 2009; Unwin & Deb, 2010). As advised by the Guideline Development Group (GDG), any study that included less than 10 participants in their study was excluded from the systematic reviews. In this chapter, Table 19.1 summarises the overall findings in terms of total number of papers included in the systematic reviews on different psychotropic medications. In this chapter findings from the randomised controlled trials (RCTs) of antipsychotics have been presented in some details and the rest of the studies are summarised in the respective tables.

Antipsychotic Medications

As expected the highest number of studies found in the systematic reviews was on antipsychotics. Here only the RCTs based on the new generation of antipsychotics are summarised. Among the new generation of antipsychotics, risperidone is studied most frequently as this is the most commonly used antipsychotic in the UK for the management of problem behaviour in ID. Further information on the effectiveness of antipsychotic medications for the management of problem behaviours in adults with ID is provided in Deb,

Table 19.1 Summary findings of systematic reviews of different psychotropic medications

Drug	*N*	RCT (number of participants included in different studies)	Prospective (number of participants included in different studies)	Retrospective (number of participants included in different studies)
Antipsychotics	12	3 (39 vs. 38; 30; 28 vs. 29 vs. 29)	6 (15, 15, 18, 20, 33, 34)	3 (17, 20, 24)
Antidepressants	10	1 (10)	7 (10, 14, 15, 16, 19, 20, 60)	2 (14, 33)
Antiepileptics	4	1 (10)	1 (28)	2 (22, 28)
Lithium	4	3 (20 vs. 22; 52; 26)	0	1 (74)
Naltrexone	4	2 (33, 24)	1 (15)	1 (56)
Psychostimulants	0	0	0	0
Antianxiety/buspirone	1	0	1 (26)	0
Diet/vitamins	1	1 (Pica: 128, control: 30)	0	0

Sohanpal, Soni, Unwin, and Lenôtre's (2007) systematic review. Further information on the effectiveness of antipsychotic medication in children with ID is presented in Unwin and Deb's (2011) recent systematic review.

There are three RCTs among adults with ID (Gagiano, Read, Thorpe, Eerdekens, & Van Hove, 2005; Tyrer et al., 2008; van Den Borre et al., 1993). There are six RCTs among children with ID with or without Autistic Spectrum Disorder (ASD) (Aman, De Smedt, Derivan, Lyons, & Findling, 2002; Buitelaar, van der Gaag, Cohen-Kettenis, & Melman, 2001; Research Unit of Pediatric Psychopharmacology-RUPP, 2002; Shea et al., 2004; Snyder et al., 2002; Van Bellinghen & De Troch, 2001). RUPP (2002) and Shea et al. (2004) primarily included children with ASD, some of whom also had ID, whereas Aman et al. (2002) and Snyder et al. (2002) primarily included children with ID but excluded those who had ASD. Of these four studies, only the RUPP study (2002) was not sponsored by a pharmaceutical company. Three of the RCTs involving children were continued for many weeks using open-label designs (Findling, Aman, Eerdekens, Derivan, & Lyons, 2004; RUPP Continuation Study, 2005; Turgay, Binder, Snyder, & Fisman, 2002).

Adult Studies

van Den Borre et al. (1993) included 37 adults (15–58 years) with ID in their study who showed aggression, SIB, agitation, hyperactivity and irritability. It is not clear whether or not the authors excluded participants who had a diagnosis of psychiatric disorder. Risperidone ($N=30$ after seven drop outs) 4–12 mg/day was used as an add-on to the existing medications. A crossover RCT design was used, which included 1 week wash out followed by 3 weeks RCT followed by 1 week wash out followed by 3 weeks crossover RCT. Primary outcome measure was Aberrant Behaviour Checklist (ABC) total score. Secondary outcome measures included Clinical Global Impression (CGI), Visual Analogue Scale (VAS) (target behaviours), extrapyramidal symptoms (Extrapyramidal Symptoms Rating Scale: ESRS), blood tests, electroencephalograph (ECG) and the participants' weight.

In the first phase there was 16 % drop in the total ABC score in the risperidone group and 15 % in the placebo group. In the second phase there was 27 % drop in the total ABC score in the risperidone group and 0 % in the placebo group. The difference in phase one was not statistically significant but the difference in phase two was. There was statistically significant improvement in the risperidone group according to CGI ($p<0.01$) (both phases). However, there was no statistically significant change according to VAS. There was also no change between the two groups in the ECG or the ESRS score. However, the participants in the risperidone group showed sedation 10 times more commonly than the placebo group. Blood tests did not detect any statistically significant change in the two groups.

Risperidone was found to be more efficacious in this study. However, conflicting results were found in two phases of the study in that two groups did equally well in phase one and the risperidone group did better only in phase two. It is therefore possible that the same group of participants continued to show improvement irrespective of the intervention used. There was also conflicting results found according to different outcome measures. For example, the risperidone group did better according to the total ABC score and CGI, but not according to VAS.

The other problems with the study included a very short wash out period, which also increased the chance of contamination from potentially withdrawal symptoms as being rated as problem behaviour, and short follow-up period. Authors did not clarify how many participants were included in each group. The method of randomisation and blinding were not described, and the IQ level or gender ratio was not specified in the paper. The total score of ABC is not valid; hence, most studies now use the Irritability (ABC-I) subscale. As authors did not exclude underlying psychiatric disorders, it is possible that in some cases, risperidone may have improved behaviour by treating the underlying psychiatric disorder. The dose of risperidone is higher than what is usually used for problem behaviour now.

Gagiano et al.'s (2005) study included 77 adults (18–57 years) with ID who did not have a diagnosis of psychiatric disorder. The first phase of the study was a parallel design RCT in which 39 participants were randomly allocated to the risperidone group and 38 into the placebo group. The RCT lasted for 4 weeks after which 58 participants continued to receive risperidone in an open-label design for another 48 weeks. Participants received risperidone as an add-on to other medications at a dose of 1–4 mg/day (mean dose: 1.8 mg/day) both in the RCT and in the open-label study.

The primary outcome measure was the ABC total score, and secondary outcome measures included Behavior Problems Inventory (BPI), CGI-S and VAS (target behaviours). According to the authors, 52 % in the risperidone group improved as opposed to 31 % in the placebo group (number needed to treat; NNT = 5). There was a statistically significant improvement in the ABC total score in the risperidone group compared with the placebo group ($p = 0.036$) and also according to CGI ($p < 0.05$). In the risperidone group, 23–41 % complained of somnolence and mean weight gain was 3.8 ± 0.6 kg. There was no difference between the groups in the QTc interval according to ECG and extrapyramidal symptoms according to the ESRS.

Overall this is a good quality study and supports the use of risperidone among adults with ID, included a reasonable number of participants (although the study could still be underpowered!), the overall design was good. However, the ABC total score lacks validity, and ABC-I score instead should have been used as the primary outcome measure. The follow-up period in the RCT of 4 weeks is short. The pharmaceutical company sponsored the study.

Tyrer et al. (2008) in a multicentre parallel design RCT randomly allocated 86 adults with ID and aggressive challenging behaviours into three groups, namely, risperidone (mean dose of 1.07–1.78 mg/day), haloperidol (mean dose of 2.5–2.94 mg/day) and placebo. Clinical assessments of aggression, aberrant behaviour, quality of life, adverse drug effects and carer burden, together with measurement of total costs, were recorded at 4, 12 and 26 weeks. The primary outcome was change in aggression after 4 weeks treatment according to the Modified Overt Aggression Scale (MOAS).

Aggression declined dramatically with all three treatments by 4 weeks, with placebo showing the greatest reduction according to MOAS median score (79 % as opposed to 57 % for combined medication groups) ($p = 0.06$). Placebo treatment was also cheaper than the other two treatments over a 6-month period in terms of total costs (Tyrer et al., 2009).

However, the risperidone group showed a higher level of aggression at the baseline compared with the placebo group and had the highest level of improvement according to the ABC-I subscale. The period of follow-up of 4 weeks when the data were analysed was short and the participant number is small, which may not have provided adequate power to the study.

Children Studies

Aman et al.'s (2002) study included 115 children (87 included) (5–12 years) with ID. The authors have excluded children with ASD. A multicentre parallel design RCT was used in which 43 children were randomly allocated to risperidone group in order to receive 1.2 mg/day mean dose and 44 allocated to the placebo group. Children were followed up for 6 weeks at the end of which Nisonger Child Behavior Rating Form (conduct problem subscale) (NCBR-F) was used as the primary outcome measure along with ABC-I, BPI, VAS and CGI as secondary outcome measures. According to the authors, 15.2 % of children in the risperidone group as opposed to 6.2 % in the placebo group showed significant improvement. Adverse effects in the risperidone group included headache and somnolence, but not extrapyramidal symptoms. Mean weight gain in the risperidone group was 2.2 kg as opposed to 0.9 kg in the placebo group.

Overall this seems to be a good quality study and supports the use of risperidone among children. However, the study could still be underpowered and the follow-up period was short. The improvement was not defined.

Findling et al. (2004) followed up 107 children from Aman et al.'s (2002) study in an open-label study for 48 weeks' extension. The same outcome measures as in Aman et al.'s (2002) study were included such as NCBR-F, ABC-I, CGI-I, BPI and VAS. Fifty (47 %) children completed the trial. Improvement with risperidone at 1.51 mg/day mean dose was maintained for 48 weeks. Although the dropout rate was high, they are not always necessarily due to the adverse effects of risperidone.

RUPP (2002) study included 101 children (5–17 years) with ASD, 74 of whom had ID and 12 borderline intelligence. The authors used multicentre parallel design RCT for 8 weeks in which 49 children were randomised to receive 0.5–3.5 mg/day mean dose of risperidone and 52 to receive placebo. The primary outcome measure was ABC-I and the secondary measure was CGI-I.

In the risperidone group, there was 57 % mean reduction in the ABC-I score at follow-up as opposed to 14 % in the placebo group ($p<0.001$). Similarly 69 % in the risperidone group and 12 % in the placebo group, respectively, showed much or very much improvement according to CGI ($p<0.001$). Average weight gain for the risperidone group was 2.7 ± 2.9 kg as opposed to 0.8 ± 2.2 kg in the placebo group ($p<0.001$). A higher proportion of children in the risperidone group reported increased appetite, fatigue, drowsiness, dizziness and drooling ($p<0.05$). In the subsequent open-label study, two-thirds of subjects with a positive response to risperidone at 8 weeks maintained the improvement at 6 months.

Overall this is a good quality study and supports the use of risperidone among children. Cohort size is still relatively small and the follow-up period is relatively short.

RUPP Continuation (2005) study was conducted in two phases. In phase one, 63 children (5–17 years) with ASD (53 with ID and seven with borderline intelligence) continued to receive risperidone at a mean dose of 1.96 mg/day in an open-label trial for 4 months. In phase two, 38 children with ASD (31 with ID and five with borderline intelligence) were allocated randomly in a double blind study either to continue to receive risperidone or being replaced by placebo for 8 weeks. The ABC-I subscale was used as the main outcome measure.

At the end of phase one, the change in ABC-I score was small and nonsignificant and the average weight gain was 5.1 kg ($p<0.001$). In phase two, 63 % of the children showed relapse in problem behaviour in the gradual placebo substitution group as opposed to the 13 % that continued to receive risperidone.

Risperidone showed persistent efficacy and good tolerability for intermediate length of treatment for children with ASD and ID. It seems that the adverse effect such as somnolence disappeared after a few weeks, but the problem with weight gain persisted. It is not clear whether or not the authors took into account the behavioural adverse effect of withdrawal, which may disappear after a few weeks.

Shea et al.'s (2004) study included 79 children (5–12 years) with ASD of whom 42 had ID and ten with borderline intelligence. The authors used a multicentre parallel design RCT in which 40 children were randomly allocated to receive 1.17 mg/day mean dose of risperidone and 39 to receive placebo for 8 weeks. ABC, NCBR-F, VAS, CGI-C and safety measures were used as outcome measures.

The children in the risperidone group showed 64 % improvement in the ABC-I score as opposed to 31 % in the placebo group ($p<0.01$). The authors also reported significant improvement in the risperidone group according to all ABC subscales, NCBR subscales and VAS. There was CGI global improvement in 87 % of the risperidone group as opposed to 40 % in the placebo group ($p<0.001$). Adverse effects, particularly the extrapyramidal symptoms, were comparable between the two groups. However, mean weight gain in the risperidone group was 2.7 kg as opposed to 1 kg in the placebo group, and somnolence was reported by 78 % of the risperidone group as opposed to 8 % in the placebo group.

Overall this is a good quality study and supports the use of risperidone among children. However, the study sample was relatively small and the follow-up period relatively short. One major criticism of the study is that the children were excluded if they did not respond to risperidone previously. This is likely to produce a major bias in the study. Also there was no correction for multiple testing (Type I error).

Snyder et al. (2002) included in their study 110 children (5–12 years) with ID (52 %) and borderline intelligence (48 %). In a 6-week parallel design RCT, the authors randomised 53 children to receive risperidone at a mean daily dose of 0.98 mg (range 0.4–3.8 mg/day) and 57 children to receive placebo.

NCBR-F-conduct behaviour subscale, ABC, BPI, VAS, CGI and cognitive assessments were used as outcome measures. There was 47 % reduction in the NCBR-F subscale score in the risperidone group as opposed to 21 % in the placebo group ($p<0.001$). The authors also reported a significant improvement in the risperidone group according to all ABC subscales, BPI ($p<0.01$), VAS ($p<0.001$) and CGI ($p=0.001$). The common adverse effects in the risperidone group included weight gain of 2 kg ($p<0.001$), somnolence, headache, appetite increase and dyspepsia. Extrapyramidal symptoms were also more common (13 %) in the risperidone group as opposed to placebo group (5 %) ($p=0.25$).

Overall this is a good quality study and supports the use of risperidone among children. However, the cohort size was relatively small and the follow-up period was short.

Turgay et al.'s (2002) study is the continuation of Snyder et al.'s study (2002). The authors continued to prescribe risperidone on an average dose of 1.38 mg/day to 77 children (5–12 years) with ID and borderline intelligence for 48 weeks in an open-label design. The authors were particularly interested to assess the long-term adverse effects of risperidone among children with ID.

Over the study period, 52 % complained of somnolence, 38 % headache, 36 % weight gain (mean gain was 7.1 kg) and 27 % increased appetite. Prolactin level peaked at 4 weeks and then came down to normal. Extrapyramidal symptoms affected 26 % of the children (mild/moderate). No change was observed in cognitive measures, haematology, vital signs and ECG. Improvement in behaviour was maintained over the 48 weeks of the study.

According to this study, risperidone showed persistent efficacy and good tolerability for intermediate length of treatment for children with ID. Somnolence and weight gain were the common adverse effects. Authors did not check for lipid profile and glucose intolerance.

Two smaller RCTs that included 38 children and adolescents (Buitelaar et al., 2001) and 13 children with ID and ASD (Van Bellinghen & De Troch, 2001) also showed significant improvement in problem behaviour in the risperidone group when compared with the placebo group.

McDougle et al. (1995) in a placebo-controlled RCT included 31 children with ASD, many of whom also had ID. Risperidone (1–6 mg/day) was compared with placebo for the management of repetitive behaviour, SIB, aggression and autism symptoms. Nine out of the 11 participants with ID in the risperidone group improved compared with two out of 13 in the placebo group. Overall, risperidone was found to be superior to placebo on all measures. Mild sedation was reported with risperidone.

Aripiprazole

So far only a handful of papers have been published on the efficacy of aripiprazole in the management of problem behaviour in people with ASD, some of whom also have ID. All these papers are published from the USA and included only children with ASD and no adults. Of these studies, only two are RCTs, both of which are conducted by the pharmaceutical company that produces aripiprazole.

Owen et al. (2009) studied the effect of aripiprazole on the irritability and challenging behaviour in 98 children with ASD in a placebo-controlled RCT over 8 weeks. Aripiprazole showed significant decrease in ABC-I score and significantly greater improvement in CGI-I compared with the placebo group.

Marcus et al. (2009) studied 218 children aged 6–17 years with ASD in a placebo-controlled RCT for the management of irritability. The aripiprazole group showed significant improvement according to the irritability, stereotypy and hyperactivity subscale of ABC. The aripiprazole group also showed significantly greater improvement in CGI and the quality-of-life measures.

Summary

Most evidence for the new antipsychotic medications was based on RCTs on risperidone apart from two RCTs on aripiprazole. There are also some RCTs conducted on the older antipsychotics such as chlorpromazine and haloperidol (see Table 19.2). It appears from the RCTs available so far that there is at present equivocal evidence for the efficacy of risperidone among adults with ID with problem behaviours, two studies showing positive and one showing negative findings. According to the evidence based on studies on children with ID (with or without ASD), risperidone seems to be effective in the management of problem behaviours. However, the main concern about using risperidone is its adverse effects such as somnolence and weight gain (not much evidence is available from the RCTs on other adverse effects such as metabolic and cardiac). Long-term follow-up studies among children are reassuring, showing that initial improvement continues over many weeks and overall, the adverse effects are tolerable.

Table 19.2 Number of studies using older antipsychotic medications

Type of problem behaviour studied (number of studies)	Range of number of participants included in different studies	Randomised
SIB (>21)	1–141	2
Stereotypy (14)	1–100	11
Aggression (22)	3–316	6
Hyperactivity (26)	6–396	10

Antidepressants

On the whole, ten studies were found in the systematic review (see Table 19.3 for the characteristics of these studies). Further information on the antidepressants is provided in the systematic review by Sohanpal et al. (2007).

Of these studies, there was one RCT (Lewis et al., 1995), which investigated the effectiveness of the tricyclic antidepressant clomipramine. The remaining studies explored the effectiveness of selective serotonin reuptake inhibitors (SSRIs). One cohort study (Troisi et al., 1995) and two open trials (Cook et al., 1992; Markowitz, 1992) looked at the efficacy of fluoxetine. Of the prospective case-series studies, there was one regarding fluoxetine (Bodfish & Madison, 1993), two on fluvoxamine (La Malfa et al., 1997, 2001) and one on paroxetine (Davanzo et al., 1998). In addition, there was one retrospective, uncontrolled study on paroxetine (Janowsky et al., 2005) and one on both paroxetine and fluoxetine (Branford et al., 1998).

Summary

The existing evidence on the use of antidepressants for the management of problem behaviour in adults with ID is scant. The study on clomip-

Table 19.3 Summary of systematic review on antidepressants

Author/evidence category (EC)	Medication/average daily dose	Target behaviour	Type of study	*N*/duration of follow-up (FU)	Outcome measures	Results
Troisi, Vicario, Nuccetelli, Ciani, and Pasini (1995), EC III	Fluoxetine 20 mg (as add-on)	Aggression (all had co-morbid epilepsy)	Prospective uncontrolled	*N* = 19/FU: overall median of 36 weeks	Modified Overt Aggression Scale (MOAS)	In 47 % there was deterioration, 42 % showed no appreciable change and 11 % had some improvement
Bodfish and Madison (1993), EC III	Fluoxetine dose range 20–80 mg (as add-on)	Compulsive behaviour, SIB, aggression (5 had co-morbid epilepsy)	Prospective uncontrolled	*N* = 16/FU: 4 months	Unspecified outcome measure; documentation of discrete episodes of target behaviour	44 % were classified as responders. 67 % of non-responders had increased mean level of target behaviour
Cook, Rowlett, Jaselskis, and Leventhal (1992), EC III	Fluoxetine dose range 20–80 mg (as add-on)	Perseverative behaviours including SIB to complex rituals (2 had co-morbid psychiatric illness)	Prospective uncontrolled	*N* = 23 but 10 applicable adults/ FU: variable—7–467 days	CGI	60 % improved, 40 % showed no improvement
Markowitz (1992), EC III	Fluoxetine dose range 20–40 mg (as add-on)	Aggression, SIB, obsessive-compulsive behaviours, social relatedness (most had co-morbid psychiatric illness)	Prospective uncontrolled	*N* = 20/FU: 3 months	Direct caretaker observation	60 % markedly improved, 20 % moderately, 10 % mildly, 10 % had no improvement and 5 % discontinued due to adverse effects
La Malfa, Bertelli, and Conte (2001), EC III	Fluvoxamine 250 mg	Aggression, aversive behaviour	Prospective uncontrolled	*N* = 60/FU: 6 weeks	Handicaps, behaviour, and skills schedule (HBSs), DOTES	Severity of aggression decreased with medication
La Malfa, Bertelli, Ricca, Mannucci, and Cabras (1997), EC III	Fluvoxamine 300 mg	Aggression, SIB	Prospective uncontrolled	*N* = 14/FU: 6 weeks	3-hourly functional analyses, CGI, PIMRA, DASH	Functional analysis showed decrease in aggression and DASH SIB score showed reduction. CGI showed improvement after 4 weeks of treatment

Lewis, Bodfish, Powell, and Golden (1995), EC I	Clomipramine titrated up to 225 mg (add-on in *N*=4) vs. placebo	Stereotypy, repetitive SIB and compulsive behaviour	RCT crossover	*N*=10/FU: 19 weeks	ABC, 5-point Likert scale for intensity of repetitive behaviour, treatment emergent side effects scale	Improvement was seen in body and object stereotype behaviours. Six improved in 1 or more repetitive behaviours
Janowsky, Shetty, Barnhill, Elamir, and Davis (2005), EC III	Paroxetine dose range 10–40 mg (as add-on)	Aggression towards others, SIB, destructive behaviours	Retrospective uncontrolled	*N*=38 but 14/relevant FU: 6 months	Psychologists' target behaviour ratings, 7-point rating scale for global and specific maladaptive behaviours	SIB and destruction/ disruptive behaviour ratings significantly decreased, aggression ratings did not significantly decrease
Branford, Bhaumik, and Naik (1998), EC III	Paroxetine dose range 20–40 mg and fluoxetine dose range 20–80 mg (add-on for both)	Perseveration of rituals, maladaptive behaviour such as aggression and SIB (10 had co-morbid epilepsy)	Retrospective Uncontrolled	*N*=33/FU: –	CGI	Overall SSRIs showed in 40 % of cases no benefit, 24 % deteriorated and 36 % had a reduction in perseverative and maladaptive behaviour
Davanzo, Belin, Widawski, and King (1998), III	Paroxetine 35 mg (add-on in *N*=8)	Aggression, SIB	Prospective uncontrolled	*N*=15/FU: 4 months	Observations of severity and frequency of target behaviours	Only severity, not frequency of aggression reduced over the whole treatment period

EC—I, randomised controlled trial (RCT); II, controlled study without randomisation; III, other nonexperimental studies such as case series, *SIB* self-injurious behaviour, *ABC* Aberrant Behaviour Checklist, *CGI* Clinical Global Impressions Scale, *DOTES* Dosage Record and Treatment Emergent Symptom Scale, *PIMRA* Psychopathology Instrument for Mentally Retarded Adults, *DASH* Diagnostic Assessment for the Severely Handicapped

ramine showed beneficial effects (Lewis et al., 1995), but the cohort size was very small ($N = 10$). However, responses to the SSRIs were varied; whereby some studies reported clear favourable results (Janowsky et al., 2005; La Malfa et al., 1997, 2001; Markowitz, 1992), some showed negative effects (Bodfish & Madison, 1993; Branford et al., 1998; Troisi et al., 1995) and other studies demonstrated both positive and negative outcomes (Cook et al., 1992; Davanzo et al., 1998). This discrepancy in findings, therefore, makes it difficult to come to a definite conclusion regarding the effectiveness of antidepressants in this context.

Improvements were largely reported in SIB and perseverative/compulsive behaviours. It may, therefore, be the case that medications were in actual fact treating underlying behaviours that are part of the Obsessive Compulsive Disorder (OCD) spectrum for which SSRIs are indicated anyway. Not surprisingly the antidepressants were most effective in the management of problem behaviour when depression or anxiety was present in the background. In a number of cases, deterioration in behaviour is reported which may have been caused by the adverse effects of some of the antidepressants.

In general, the majority of the evidence based on open trials and case-series studies was fraught with methodological concerns. The small sample sizes meant that the studies were statistically underpowered and often control groups were not recruited. There was a dearth of validated outcome measures utilised and where more than one assessor conducted the outcome measurements, inter-rater reliability was not contemplated.

The efficacy of antidepressants certainly deserves more attention in research, as there is evidence to suggest (Unwin et al., 2011) that these medications are used commonly in the management of problem behaviours in people with ID. This review does not suggest that they are ineffective but that there is not enough good quality evidence for their usefulness at present.

Mood Stabilisers (Lithium and Antiepileptic Medication)

Summary of the findings from the mood stabiliser systematic review is presented in Table 19.4. Further information on the effectiveness of mood stabilisers is presented in Deb et al.'s systematic review (2008). Eight studies on mood stabilisers were extracted through the systematic reviews, one of which on lithium (Tyrer et al., 1993) was published in a book, which was not peer reviewed. The other four studies included one retrospective case-series study on lithium (Langee, 1990). There were one prospective (Verhoeven & Tuinier, 2001) and another retrospective (Ruedrich et al., 1999) case series, both on the effectiveness of sodium valproate. The fourth was a retrospective study of effectiveness of topiramate in the management of problem behaviours in adults with ID (Janowsky et al., 2003). Two further studies explored the effects of lithium, one of which consisted of adults and children with ID (Tyrer et al., 1984) and the other adults only (Craft et al., 1987). The third relevant study was on carbamazepine (Reid et al., 1981).

Summary

There are only a small number of RCTs on mood stabilisers primarily on lithium. However, the RCTs on lithium are dated and of poor quality as they included primarily inpatients, included small number of patients and used questionable outcome measures that are not validated. Some studies showed effectiveness of lithium on particular problem behaviours, but not on others. There is also a major concern for using lithium on patients with severe ID who cannot consent to treatment because once started it is difficult to withdraw lithium. Therefore, it may not be ethical to prescribe lithium to someone who cannot consent to a treatment which has potential long-term major adverse effects and narrow window between therapeutic serum level and toxic level.

Table 19.4 Summary findings of systematic review of mood stabilisers (lithium and antiepileptic medications)

Author/evidence category (EC)	Medication/average daily dose	Target behaviour	Type of study	*N*	Outcome measures	Results
Tyrer, Aronson, and Lauder (1993), EC II	Lithium 500 mg adjusted to achieve 0.5–0.8 mmol/L plasma levels	Aggression, SIB, destructive behaviour, tantrums, hyperactivity	Controlled, crossover	52	VAS	54 % improved on lithium, 44 % unchanged and 2 participants dropped out
Langee (1990), EC III	Lithium dosage adjusted to achieve 0.7–1.2 mmol/L plasma levels	Aggression, SIB, hyperactivity	Retrospective uncontrolled	66	Behaviour disturbance index (severity × frequency)	47 % improved of whom 77 % required additional medication and 53 % remained unchanged
Craft et al. (1987), EC I	Lithium dosage adjusted to achieve 0.7–1.0 mmol/L plasma levels	Aggression	Controlled, crossover	Study group: 22, controls: 20	Scores of counts of frequency and severity of target behaviour	73 % improved, 9 % got worse and 18 % remained unchanged. 30 % improved on placebo
Verhoeven and Tuinier (2001), EC III	Sodium valproate 1,345 mg	SIB, aggression, hyperactivity, disorganised behaviour, Stereotypies, impulsivity	Prospective uncontrolled	28	VAS, CGI	68 % showed some degree of improvement and 32 % minimally improved or remained unchanged
Ruedrich, Swales, Fossaceca, Toliver, and Rutkowski (1999), EC III	Sodium valproate 920 mg	Various but primarily SIB and aggression	Retrospective uncontrolled	28	Monthly behaviour counts, CGI	71 % markedly improved, 21 % mildly improved, 1 remained unchanged and 1 got worse
Janowsky, Kraus, Barnhill, Elamir, and Davis (2003), EC III	Topiramate 202 mg	Aggression, SIB, destructive/disruptive behaviour	Retrospective uncontrolled	22	Cumulative frequency recordings, global severity ratings	74 % improved, 1 remained unchanged and 4 got worse
Reid, Naylor, and Kay (1981), EC II	Carbamazepine 25–26 µg/L	Overactivity	Controlled, crossover	10	Nurse's behaviour ratings	Overall, 40 % improved on carbamazepine and 40 % on placebo
Tyrer, Walsh, Edwards, Berney, and Stephens (1984), EC II	Lithium 500 mg adjusted to achieve 0.5–0.8 mmol/L plasma levels	Aggression	Controlled, crossover	26	VAS, nurse behaviour ratings	68 % improved on lithium

Evidence categories—I, randomised controlled trial (RCT); II, controlled study without randomisation; III, other nonexperimental studies such as case series, *SIB* self-injurious behaviour, *VAS* Visual Analogue Scale; *CGI* Clinical Global Impressions Scale

In some people with severe and profound ID, it may not be possible to carry out blood tests that are mandatory. There are also potentially less toxic alternatives to lithium available which may not require regular blood tests. Within this context it is difficult to recommend lithium for use in people with severe and profound ID unless absolutely necessary. In Unwin et al.'s (2011) prospective 12-month follow-up study, there is little evidence of the use of lithium by the UK psychiatrists. Unfortunately currently there is not much evidence for the effectiveness of other mood stabilisers such as sodium valproate, carbamazepine and lamotrigine, which may provide a better alternative to lithium. However, lack of evidence does not mean that there is evidence that these antiepileptic mood stabilisers are not effective in the management of problem behaviour in people with ID.

Antianxiety Medications/ Beta-Blockers

King and Davanzo (1996) reported in a prospective uncontrolled study of 26 adults with ID (age range 25–63 years) (46 % male) of the effect of buspirone 25–60 mg/day (average 52 mg/day) on aggression and/or SIB. This study did not show any improvement from buspirone.

Summary

There is little evidence currently to recommend any antianxiety medication for the long-term management of problem behaviours in people with ID. The benzodiazepine group of medications carries the risk of tolerance and dependence in the long run. The evidence for the effectiveness of buspirone is currently poor, therefore, cannot be recommended. However, for the general population, some SSRIs, SNRI, pregabalin and quetiapine are now recommended treatment for anxiety-related disorders (Bandelow et al., 2008; NICE guide on the management of anxiety disorders; www.nice.org.uk). In the field of ID, some antipsychotics are prescribed in a smaller than antipsychotic dose to manage problem behaviours with the assumption that at a lower dose, antipsychotics work as an antianxiety medication, although the evidence to support this assumption currently is not available from the literature.

Opioid Antagonists

On the whole, four studies were found in the systematic review on the opioid antagonists that included adults (see Deb & Unwin, 2007b). Three of the studies were prospective trials (Sandman et al., 1993, 2000; Willemsen-Swinkells, Buitelaar, Nijhof, & Van Engeland, 1995) and one was a retrospective case-series study (Casner, Weinheimer, & Gualtieri, 1996). Only one study on children (Campbell et al., 1993) is described in this chapter. The characteristics of these studies are summarised in Table 19.5.

Summary

There are only a handful of RCTs on naltrexone that included a small number of participants, different doses and crossover design, which has its drawbacks. The findings are equivocal in that some showed beneficial effect from naltrexone and others did not. One study showed differential effect depending on the dose, particularly the higher dose being effective and lower doses being noneffective.

Psychostimulants

Most studies of psychostimulants have been used on people with a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD). Therefore, almost all the studies used ADHD symptoms as outcome measures than problem behaviour per se, although problem behaviours are often included in the outcome measures as part of the ADHD symptoms. Therefore, it is difficult to find any evidence to prove effectiveness of psychostimulants specifically for the management of problem behaviour per

Table 19.5 Summary of findings from systematic review on the opioid antagonists

Author/evidence category (EC)	Medication/average daily dose	Target behaviour	Type of study	*N*	Outcome measures	Results
Sandman et al. (2000), EC III	Naltrexone single dose 0.5, 1.0 or 2.0 mg/kg	SIB	Double blind, prospective (follow-up of Sandman et al., 1993)[a]	15 (including 1 under 18 years of age)	Direct observations	Subgroup of participants showed a decrease in SIB for 1 year after acute exposure to naltrexone. Five showed an increase in SIB after long-term treatment
Casner et al. (1996), EC III	Naltrexone 96.8 mg	SIB	Retrospective uncontrolled	56	Retrospective review of behavioural data	57 % responded to naltrexone. Blind review showed a 50 % reduction in SIB in 25 % of participants
Willemsen-Swinkells et al. (1995), EC I	Naltrexone *N* = 19: 50 mg, *N* = 14: 150 mg	SIB	Controlled, crossover	33	ABC, CGI, target symptom checklist, some had direct observations	No therapeutic effect with naltrexone
Sandman et al. (1993), EC III	Naltrexone doses of 0.5, 1.0 and 2.0 mg/kg	SIB	Prospective trial[a]	24 (including 1 under 18 years of age)	Direct observations, ONE, adapted version of Conners' Parent-Teacher Questionnaire, SOME, DISCUS, stereotypies checklist	Naltrexone decreased SIB by 50 % at a dose of 2 mg/kg in 52 % of participants. Single-dose effect of at least a 25 % reduction was apparent in 86 %
Campbell et al. (1993), EC I	Naltrexone 1 mg/kg	Aggression	RCT	Study group: 23, controls: 18	CGI and NGI combined to give Global Clinical Consensus (GCC), aggression rating scale, naltrexone side effects checklist	No therapeutic effect with naltrexone

Evidence categories—I, randomised controlled trial (RCT); II, controlled study without randomisation; III, other nonexperimental studies such as case series, *SIB* self-injurious behaviour, *ABC* Aberrant Behaviour Checklist, *CGI* Clinical Global Impressions Scale, *ONE* Objective Neurological Examination, *SOME* Summation of Maladaptive Expression, *DISCUS* Dyskinesia Identification System—Condensed User Scale

[a]No comparison was made between treatment vs. placebo and, hence, these trials cannot be allocated an evidence category rating of II or I

se in people with ID without a diagnosis of ADHD. One study by Aman and Singh (1982) used an RCT design to compare methylphenidate with placebo for the management of different problem behaviours among 28 participants (age 13.6–26.4 years) with ID. Overall no significant effect was found from the medication.

Vitamins and Others

The only study available on the effectiveness of diet (zinc supplement) on the management of problem behaviour (pica) did not include a proper placebo control group (Lofts, Schroeder, & Maier, 1990). Therefore, it is difficult to draw any conclusion from this study on the effectiveness of diet.

Conclusion

The evidence presented in this chapter on the effectiveness of psychotropic medications has to be interpreted with caution. Most studies in this field are case reports on a small number of participants. It is known that studies with positive findings are more likely to be published than studies with negative findings. This is likely to create a reporting bias for the published case reports. There are only a few RCTs, but they often used a small cohort size, resulting in insufficient statistical power to draw firm conclusions. The outcome measures used are often not appropriate or validated. The method of selection of the control and the experimental group is not always clear or appropriate, and outcome data are often not presented in an appropriate manner. For example, most studies neither quote the 'number needed to treat' (NNT) nor use analysis based on the 'intention to treat' (ITT) model. Most studies do not distinguish symptoms of psychiatric illness from those of problem behaviours, and often researchers do not take into account the existence of autistic and ADHD symptoms in the context of problem behaviour. Also in many studies, participants with comorbid psychiatric disorders were not excluded. It, therefore, remains unclear whether the psychotropic medications used in these studies treated the underlying psychiatric condition or the problem behaviour per se. It is important, however, to recognise the difficulty in carrying out RCTs involving people with ID (Oliver-Africano et al., 2010), particularly because of securing consent in adults who lack capacity. Subsequently these people are deprived of the opportunity to have treatments that are based on strong evidence.

Problem behaviours are usually long-standing; therefore, short follow-up periods used in most studies meant that it is not possible to know whether patients would derive any benefit in the long term. Only a long-term follow-up will determine the effect of many confounding factors such as environmental changes that are concomitant with the use of psychotropic medications. Most studies do not take into account the confounding effect of concomitant non-medication-based management of behaviour, which may have a profound effect on the behaviour. Similarly in most studies the antipsychotics were used as an add-on therapy, which made it difficult to tease apart the confounding effects of the other medications that have been used simultaneously. For example, the use of antiepileptic medications is common among adults with ID (Deb, 2007) and these medications may have an effect on the behaviour. However, an RCT design should take care of some of these confounding factors.

Another problem of interpreting the case report-based data is that many patients who showed improvement on a particular medication may have had an unsuccessful trial of other medications that have been shown to be effective in other case studies. Therefore, the individualised response to specific medication is always going to be difficult to determine. There may be many causes for problem behaviours among people with ID and many factors including medical, psychological and social may influence behaviour. It is, therefore, imperative to carry out a detailed assessment of the causes and consequences of problem behaviours before an intervention is implemented. However, none of the studies provide any detail of behaviour analysis. This sort of issue could be addressed by including an overall

quality of life measure. Future studies should also assess the effect of interventions on family carers' burden and cost-effectiveness.

On the basis of the evidence available, it is difficult either to recommend or to refute the use of psychotropic medications for the management of problem behaviours in people with ID. Furthermore, there is no evidence to show effectiveness of particular psychotropic medication for particular problem behaviours. In the absence of this evidence, guidelines have been developed in order to provide advice to clinicians when using psychotropic medications for the management of problem behaviours in people with ID (Banks et al., 2007; Deb, Clarke, & Unwin, 2006; Deb et al., 2009; Einfeld, 2004; Reiss & Aman, 1998; Unwin & Deb, 2010). These guides advise that a thorough assessment of the causes and effects of the problem behaviours including organic, psychiatric, psychological and social factors should be carried out before a medication is prescribed. Before initiating medication, a formulation should be documented including the assessment and a rationale for the use of medication. Non-medication-based management of problem behaviours should always be considered and be used either instead of or along with medication when necessary. People with ID and their carers as well as the multidisciplinary team should be fully involved in the decision-making process from the outset (Hall & Deb, 2008). There are accessible versions of information leaflets (with audio versions) on psychotropic medications (Unwin & Deb, 2007) freely available for downloading from the web (www.ld-medication.bham.ac.uk). These should be handed over to patients and their carers where appropriate. The time, methods and personnel to conduct the follow-up assessment should be recorded at the outset. Both the impact of the intervention on the behaviour as well as the adverse events should be assessed as objectively as possible, if necessary using validated instruments. At each follow-up, the original formulation should be reassessed; non-medication-based interventions should be considered along with the possibility of withdrawing medication. The psychotropic medication, if needed, should be used with as small a dose as possible for as short a period of time as necessary. If medication is withdrawn, a relapse plan should be in place and the possibility of withdrawal symptoms in the form of problem behaviours should be considered before taking a decision to reinstate any psychotropic medication. The ultimate aim of the management should be symptom reduction as well as to improve the quality of life of the individual with intellectual disability.

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