

# PSYCHOPHARMACOLOGICAL TREATMENTS FOR PATIENTS WITH INTELLECTUAL DISABILITY

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## ABSTRACT

The use of psychotropic drugs in intellectual disability is reviewed with reference to psychiatric illness — including psychoses, neuroses, sleep disorders, and personality disorders — as well as to acute and chronic behaviour disorder. Aberrant sexual behaviour and other relevant conditions, namely stereotypies, autism, Down's syndrome, Lesch-Nyhan syndrome, Cornelia de Lange syndrome, and Prader-Willi syndrome, are also discussed.

Recent empirical evidence from the intellectual disability literature is documented and where appropriate, recommendations are made regarding which drugs should take priority. The authors highlight the clinical importance of psychological and behavioural therapies and conclude that pharmacological treatment must be undertaken with caution for this population. In particular, physicians should make themselves especially aware of the side effects and health risks associated with psychotropic drugs.

**Key words:** *Behaviour Disorder; Developmental Disorders; Mental Retardation; Psychiatric Illness; Psychopharmacology*

## INTRODUCTION

Neuroleptic agents and other psychotropic drugs are still widely prescribed for people with intellectual disability. Between 20% and 77% of residents in institutions for intellectually disabled people receive psychotropic drugs.<sup>1,2</sup> The most frequent drugs employed are the neuroleptics although antidepressants, anticonvulsants, lithium,  $\beta$ -blockers, benzodiazepines, antimuscarinic drugs, and hypnotics are also prescribed.

There is occasional use of central nervous system (CNS) stimulants, opiate antagonists, and neurotransmitter-depleting agents such as the benzoquinolizine drug, tetrabenazine. Most patients receive more than one psychotropic drug.<sup>3</sup> The majority of people taking these drugs do not have clear psychiatric illnesses and most would be described as having a behavioural disturbance.<sup>4,5</sup>

## TREATMENT OF PSYCHIATRIC ILLNESS

### PSYCHOSES

If the patient has a psychiatric illness that fulfils International Classification of Disease (ICD) -10 or Diagnostic and Statistical Manual of Mental Disorders (DSM) -IV criteria for a psychiatric disorder for which drug treatment is effective, it is usual to give these drugs in the first instance. In practice, the majority of patients with intellectual disability do not fulfil the criteria

indicated in standard operational texts, hampering confident diagnosis of most psychiatric illnesses, in particular psychotic disorders. Thus, it is not possible to diagnose schizophrenia in those who function below the mild intellectual disability range.<sup>6</sup> However, if there is evidence of affective flattening, incongruous behaviour, self-preoccupation and catatonic posturing, neuroleptic medication can have a dramatic effect, suggesting that such syndromes in those of lower intelligence are of schizophrenic origin.<sup>7</sup>

A diagnosis of affective disorder can be made more confidently for intellectually disabled people even if they have major communication difficulties. The symptom triad of recent insomnia, loss of weight, and reduced activity usually indicates depression in the absence of a physical cause. Conversely, increasing activity accompanied by euphoria and/or irritability is suggestive of mania in the absence of other factors.

The treatment of schizophrenia in intellectually disabled persons is not essentially different from the treatment of this illness in people of average intelligence. There is increased usage of the newer 'atypical' anti-psychotic drugs in people with intellectual disability because of the dangers of tardive dyskinesia<sup>8</sup> and akathisia<sup>9</sup> that are more frequent for older neuroleptics. A further hazard is the potentially fatal neuroleptic malignant syndrome, which has also been reported following treatment with atypical neuroleptics such as clozapine and risperidone.<sup>10</sup> There has also been a recent report of neuroleptic-induced dementia in four adults with intellectual disability.<sup>11</sup>

The benzamide derivative, sulpiride, differs from other antipsychotic agents in that it acts at the pre-synaptic dopamine receptor. It is reputed to cause fewer extrapyramidal side effects and tardive dyskinesia than the older drugs although its long-term effects are yet to be reported. A valuable new drug that rarely causes tardive dyskinesia or extrapyramidal side effects is clozapine, a tricyclic drug of the dibenzodiazepine family. Successful treatment with clozapine has recently been reported by Thuresson and Farnstrand<sup>12</sup> and Boachie and McGinnity.<sup>13</sup> However clozapine causes agranulocytosis in 1% to 2% of patients<sup>14</sup> and because of this it is only licensed in the UK for the treatment of resistant schizophrenia, and even then only under carefully controlled conditions. Weekly blood counts must be monitored and the drug stopped immediately if there is a fall in total white cell count to less than  $3 \times 10^9/L$ , total neutrophil count of less than  $1.5 \times 10^9/L$ , or platelet count below  $100 \times 10^9/L$ .

Risperidone is a new neuroleptic drug that blocks dopamine  $D_2$  receptors but also has antagonist actions at the  $5HT_2$  receptor. This drug is less prone to cause movement disorders<sup>15</sup> and studies suggest that it is particularly advantageous for patients who have negative symptoms.<sup>16</sup>

Treatment strategies for intellectually disabled people who have affective disorder are not dissimilar from the treatment of these conditions for patients with average intelligence. Antidepressants are the mainstay of treatment, since there is some suggestion that drugs such as carbamazepine, which have mood stabilising effects in those of average intelligence, may be less effective in the intellectually disabled.

If antidepressants fail to relieve depressive symptoms in an intellectually disabled patient, the prescription of lithium may produce improvement within a 4-week period.<sup>17</sup> This strategy is not widely reported for patients with intellectual disability. For an extensive review of treatment for unipolar depression the reader is referred to Lund.<sup>18</sup>

For the treatment of bipolar affective disorder for intellectually disabled people, lithium is the drug of choice. However, lithium may well be less effective for intellectually disabled patients than it is for patients with average intelligence. This is probably because comparatively more individuals with intellectual disability have a quick-cycling bipolar disorder (i.e. more than four episodes in 1 year). The advantages of the combination of lithium and carbamazepine for the treatment of bipolar disorder for intellectually disabled people has been shown by Glue,<sup>19</sup> although sodium valproate may be the most effective of all the mood stabilisers.<sup>20</sup>

## NEUROSES

In general, psychotropic drugs are not used widely for the treatment of neuroses for intellectually disabled people. In many cases, neurotic symptoms in this population result from environmental changes.<sup>21</sup> If feasible, supportive psychotherapy and restoration of previous activities and relationships are the treatment of choice.

The use of drugs to control anxiety should be largely confined to the control of acute anxiety reactions. The shorter-acting benzodiazepines such as lorazepam and midazolam

should be preferred over the longer-acting drugs such as diazepam.

Prolonged treatment for anxiety is unlikely to be necessary. If long-term treatment is envisaged, benzodiazepines should not be given. Buspirone, an azaspirodecanodione, is a new anti-anxiety drug that has been used for people with intellectual disability to reduce anxiety and behavioural disturbance.<sup>22-24</sup> Propranolol and  $\beta$ -blocking agents that do not cross the blood-brain barrier such as atenolol and nadolol may be useful for patients who show sympathetic overactivity when emotionally aroused.

## SLEEP DISORDERS

As far as possible, non-drug treatment should be used for people complaining of poor sleep. If drugs are to be given, they should be given for short periods or intermittently. Zopiclone or zolpidem may be needed. Promethazine 25-50 mg or trimeprazine 20-30 mg nocte are alternatives. The sedative antidepressants such as trimipramine and trazodone are also helpful for short-term use or for intermittent therapy.

## PERSONALITY DISORDERS

There have been no controlled trials performed for the treatment of personality disorders in intellectually disabled people. For people of average intelligence, studies suggest that those with emotionally unstable personality disorder may benefit from small doses of neuroleptic drugs, lithium or monoamine oxidase inhibitors.<sup>25</sup>

## TREATMENT OF BEHAVIOUR DISORDER

The category of behaviour disorder in the field of intellectual disability is difficult to define. Although it is possible to describe reliably behaviour disturbance, the meaning of this is more difficult to determine. This is mainly because of the inability of the disabled person to effectively communicate the motives of their behaviour. Many people with intellectual disability behave impulsively without thinking of the consequences and most have been poorly trained in acceptable social behaviour. Indeed, behaviour disorder without definite evidence of psychiatric illness is the most common reason why those with intellectual disability are referred to a psychiatrist.<sup>26</sup> Before prescribing psychotropic drugs, it is instructive to determine the antecedents and the consequences of these behaviours, and the nature of the situation in which the disturbed act occurs.

As far as possible, behavioural and psychological techniques should be used for behavioural disturbance. Only if these techniques are not effective or if the environment concerned cannot be altered in any major way, should pharmacological treatment be employed. Even when drug treatment is recommended, there should be a continual search for factors precipitating aggression. For instance, many intellectually disabled people who are unable to communicate are aggressive or self-injurious when they are in pain or in distress because of medical problems.

## ACUTE BEHAVIOURAL PROBLEMS

For the pharmacological treatment of acute behavioural disturbance such as aggressive outbursts, antipsychotics and benzodiazepines are most widely employed. Chlorpromazine has been used for many years for this purpose but has the disadvantage of causing prolonged sedation and hypotension. A faster-acting drug with a shorter onset of action is droperidol, a butyrophenone. The onset of action when administered parenterally is between 3 and 10 minutes<sup>27</sup> and the sedative effects last for 2 to 4 hours. The main problems with this drug are its extrapyramidal side effects for which a muscarinic anti-Parkinson drug such as procyclidine 5 mg may be needed. Alternatively, fast-acting benzodiazepines may be given. Lorazepam and midazolam are the preferred agents because of their relatively short half-lives and lack of respiratory depression.

The paradoxical pro-aggressive effects of benzodiazepines have been overemphasised. However, these drugs can sometimes cause an increase in aggression and alternative agents should then be given. Paraldehyde is an effective drug and can be given even if liver function is impaired. However, lactic acidosis has been reported.<sup>28</sup>

## CHRONIC BEHAVIOURAL PROBLEMS

If a patient presents with chronic behavioural disturbance, it is important to rule out any underlying physical or psychiatric illness. If, having treated any underlying illness, the behavioural disturbance persists, behavioural and psychological techniques should be tried first. If these techniques fail, only then should drug treatment be undertaken if the behaviour is frequent, reduces the capacity of the individual to participate in activities which would be beneficial, and it is not possible to change environmental circumstances. The choice of drug treatment depends not only on the clinical presentation of the disturbance at interview, but also on past history, family history, and the course of the illness.

Neuroleptic drugs are most commonly used, despite the fact that there are no well-controlled trials that indicate that antipsychotic monotherapy is more effective than other agents or placebo for the treatment of disturbed behaviour in this population has been conducted.<sup>29</sup> In addition, neuroleptic drugs are known to cause tardive dyskinesia when given for long periods, particularly for patients with evidence of brain damage, suggesting that their long-term use for intellectually disabled people with behavioural disturbance without psychosis should be avoided.<sup>30</sup>

If there is evidence of recent or past mood disturbance, or if there is a periodic cycle of disturbed behaviour with affective manifestations, lithium or carbamazepine are the drugs of choice. Lithium is effective for patients with intellectual disability who show aggression towards others<sup>31,32</sup> and is the clear treatment of choice for individuals with a bipolar affective illness.<sup>33</sup> Those who show physical aggression towards others respond best to treatment.<sup>34</sup> However, lithium is a potentially dangerous drug and clinicians should be aware of the rare but real possibility of lithium toxicity if lithium levels are not carefully monitored.<sup>35</sup>

There is no firm evidence that carbamazepine is valuable for treating similar syndromes in intellectual disability unless there is an affective component. However, retrospective studies have shown that carbamazepine is more effective in reducing behavioural disturbance if there is evidence of any electroencephalogram (EEG) abnormality.<sup>36</sup>

If there are signs of adrenergic  $\beta$ -receptor overactivity such as tachycardia, tremor, palpitations, or other somatic signs of overarousal, then  $\beta$ -blocking drugs such as propranolol, nadolol, atenolol, and oxprenolol may be of value. All  $\beta$ -blocking drugs slow the heart and reduce myocardial contraction. They should not be given if the pulse falls below 48 beats per minute or if there are signs of heart failure or myocardial depression. **They should never** be used for patients with a recent history of obstructive airway disease or asthma.

Naltrexone, an opioid antagonist, has been widely canvassed as a useful agent in reducing self-injurious behaviour in severely and profoundly handicapped individuals. However, it has recently been shown to be ineffective in double-blind trials.<sup>37</sup>

Antidepressant drugs that increase the synaptic availability of serotonin (5-hydroxytryptamine [5-HT]) may reduce persistent aggressive behaviour.<sup>23</sup> The selective serotonin reuptake inhibitor (SSRI) agents such as fluoxetine and fluvoxamine are the most frequently used drugs although trazodone and the tricyclic antidepressant drug, clomipramine, have been used to good effect.<sup>38</sup> Paroxetine, a SSRI, has also recently been shown to be effective.<sup>12</sup> A new class of 5-HT<sub>1A</sub> agonists, called serenics (e.g. eltopazine) has been shown to reduce aggression in intellectually disabled people,<sup>39</sup> but do not maintain this effect over time. Other agents, including buspirone<sup>23,24</sup> and amantadine<sup>40</sup> have been successful in open trials.

In practice, however, the most frequently used drugs for intellectually disabled patients with a history of chronic behavioural disturbance are the neuroleptic drugs.<sup>4,41</sup> One of the reasons why these drugs may have been maintained is because withdrawal treatment is associated with an increase in aggressive behaviour.<sup>42</sup> However, sudden withdrawal of antipsychotic drugs, particularly those with pronounced anticholinergic effects, is associated with withdrawal symptoms, mainly nausea, anorexia, restlessness, and painful muscles.<sup>43,44</sup> These effects may contribute to aggressive behaviour in patients who cannot communicate in other ways.

## ABERRANT SEXUAL BEHAVIOUR

Sexual offences by intellectually disabled people are frequent and often lead to a request for psychiatric help.<sup>45</sup> Many of those who commit sexual offences are not fully aware of what constitutes acceptable sexual practice, and may have a normal sexual drive but poor understanding of sexual manners.<sup>45</sup> Sex education instruction packages are available and are valuable for identifying deficiencies in patients' knowledge and may indirectly help to assess the degree of motivation. Psychological and behavioural treatments have a greater

part to play than drug therapy for this condition. However, drugs may assist patients in avoiding sexual temptation. Before giving these drugs, consent must be sought.

In North America, medroxyprogesterone acetate (MPA) is used both for people with intellectual disability and those of average intelligence for recurrent exhibitionism, incest, transvestism, and other sexual disorders.<sup>46</sup>

In the UK and Europe, the anti-androgen drug cyproterone acetate is favoured over MPA. Cyproterone decreases serum testosterone and open studies have reported its efficacy in reducing masturbation, indecent exposure, and sexual offences in intellectually disabled men.<sup>47</sup> Sexual interest and sexual activity were reduced for sexual offenders receiving this drug in a controlled trial.<sup>48</sup> Cyproterone has been reported to be hepatotoxic if given in a dosage of more than 200 mg daily.<sup>49</sup>

Benperidol is also licensed for the control of deviant and antisocial sexual behaviour. However, the few double-blind investigations that have been performed do not suggest that it is an effective drug for reducing sexual desire.<sup>47</sup>

Another drug that has been used rarely in Europe is goserelin. Goserelin is a luteinizing hormone releasing hormone analogue that effectively reduces testosterone.<sup>50</sup> Although it is not licensed for the reduction of male sexual drive, it has been used effectively for this purpose.

## OTHER CONDITIONS

### STEREOTYPIES

Hyperactivity and stereotypies occasionally require treatment with drugs. Carbamazepine<sup>51</sup> and the central nervous stimulants, dexamphetamine and methylphenidate,<sup>52</sup> have been found to be more effective than placebo. Carbamazepine is probably the best first-line drug. There is good evidence that the antipsychotic drugs reduce stereotypies and their effects are greatest in the most severely affected individuals.<sup>53</sup> Clomipramine<sup>38</sup> and lithium<sup>34</sup> may also be of benefit.

### AUTISM

Before treating the autistic patient with psychotropic drugs, it is important to decide which particular symptom or feature is being addressed. The drugs indicated below are included on the basis of their effects on core autistic symptoms.

Fenfluramine, a fluorinated amphetamine that does not have the stimulant properties of its parent drug and blocks serotonin receptors, was shown to improve fundamental autistic features and behaviour.<sup>54</sup> However, a later study did not show major benefits and treatment successes were mainly related to reduction of hyperactivity and stereotypy.<sup>55</sup> The drug is no longer available for this purpose.<sup>56</sup> More promising results have been obtained using the SSRI, fluoxetine<sup>57</sup> and the experimental 5-HT<sub>1A</sub> agonist, eltoprazine,<sup>58</sup> The opiate antagonist drugs such as naltrexone have been shown to increase physical and eye contact, improve communication and reduce aggression and negativism in children and adults with autism,<sup>59</sup> but later studies were not conclusive.<sup>60,61</sup> Pyridoxine, magnesium and tetrahydrobiopterin have all been used for the treatment of autism in uncontrolled studies

but no consistent benefits have been shown. There is no drug of choice for autism. The SSRIs,  $\beta$ -blockers, and naltrexone may all be used. The specific serotonin reuptake blocking drugs may be of most benefit.

### DOWN'S SYNDROME

Individuals with Down's syndrome have reduced serotonergic turnover<sup>62</sup> and the literature suggests that these patients respond well to tricyclic antidepressants. Although mania is not widely reported in Down's syndrome,<sup>63</sup> it does occur and lithium or sodium valproate are effective drugs for controlling mania.

### LESCH-NYHAN SYNDROME

In Lesch-Nyhan syndrome, there is reduction of dopamine production, leading to dopamine D<sub>2</sub> receptor supersensitivity. The neuroleptic drug fluphenazine is shown to be valuable in reducing the self-mutilatory behaviour exhibited by patients with Lesch-Nyhan syndrome.<sup>64</sup> Other drugs such as sulphiride and pimozide may be of particular advantage for this condition.

### CORNELIA DE LANGE SYNDROME

Cornelia de Lange syndrome is another syndrome in which self-injurious behaviour is frequently reported. Isolated patients with low blood serotonin levels have been treated with serotonergic enhancing drugs, in particular trazodone combined with L-tryptophan.<sup>65</sup> Drugs that reduce arousal may help in this condition.

### PRADER-WILLI SYNDROME

Prader-Willi syndrome is manifest by excessive eating, obesity, and severe aggressive episodes. It has now been recognised that there is a disorder of satiety in these individuals and drug treatment has attempted to correct this. Fenfluramine, an appetite suppressant, was used in early studies and a recent case report suggests that fluoxetine, an antidepressant that marginally reduces weight, is effective in this condition.<sup>66</sup> Naltrexone, carbamazepine, and testosterone have also been used for this syndrome.<sup>67</sup>

## CONCLUSIONS

The use of drugs for intellectual disability should be based on accurate diagnosis and sound pharmacological principles. Guidelines to encourage rational prescribing are helpful.<sup>68</sup> If there is success with the prescribed agent; a decision should be made as to how long to maintain treatment with the drug and when or whether the dose should be reduced. It should be remembered that patients who demonstrate intermittent behavioural disturbance are likely to improve following a severe behavioural outburst and the drug that has been given to control the behaviour may not be responsible for the improvement. Above all, observed symptoms and signs should be assessed to determine how far these are due to the drugs or whether they are due to psychiatric or behavioural factors. The psychiatrist prescribing psychotropic drugs has to be much more aware of the side-effects of these drugs when treating a

population who, in the main, are not able accurately to report side-effects. This is particularly important in the light of evidence that suggests that many professionals gravely underestimate the seriousness of such side-effects.<sup>69</sup>

Once a decision has been made to treat a specific condition with drugs, there may be advantages in using combination treatments after a single agent has been used for a sufficient length of time in adequate dosage. In particular, the benefits of lithium and carbamazepine should be more widely known.

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