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Psychopharmacological Treatment of Oppositional Defiant Disorder

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Abstract

Oppositional defiant disorder (ODD) consists of an enduring pattern of uncooperative, defiant and hostile behaviour toward authority figures that does not involve major antisocial violations and is not accounted for by the developmental stage of the child. The rate of ODD in children and adolescents in the general population has been reported to be between 2% and 16%. The International Classification of Diseases 10th Revision (ICD-10) classifies ODD as a mild form of conduct disorder (CD), and it has been estimated that up to 60% of patients with ODD will develop CD. Therefore, ODD should be identified and treated as early and effectively as possible.

In more than one-half of patients with attention-deficit hyperactivity disorder (ADHD), ODD is also part of the clinical picture. There is strong evidence in the literature to suggest that ODD and ADHD overlap; many medications that are used to treat ADHD may also be efficacious in the treatment of ODD. A few studies have reported the positive effects of psychostimulants or atomoxetine in

the treatment of ODD associated with ADHD. Patients with ODD and CD with severe aggression may respond well to risperidone, with or without psychostimulants. Mood regulators, α_2-agonists and antidepressants may also have a role as second-line agents in the treatment of ODD and its co-morbidities.

This review describes the diagnosis, differential diagnosis and co-morbidities of ODD in children and adolescents. The evidence for transition of ODD to a more severe pathology such as conduct disorder (CD) is also reviewed. Questionnaires that are useful aids in the diagnosis and differential diagnosis of ODD and its treatment are outlined. The major focus is the pharmacological treatment of ODD and its common co-morbid disorders, with practical clinical suggestions provided for selecting medications for treatment.

1. Symptomatology and Diagnostic Criteria for Oppositional Defiant Disorder (ODD)

Oppositional defiant disorder (ODD) consists of an enduring pattern of uncooperative, defiant and hostile behaviour toward authority figures that does not involve major antisocial violations and is not accounted for by the developmental stage of the child. ODD is one of the most common disorders in childhood and is often associated with other mental disorders; it can result in significant functional impairment.

In the DSM-IV-TR,[1] ODD comes under the general diagnostic grouping of 'attention-deficit hyperactivity and disruptive behaviour disorders'. According to the DSM-IV-TR diagnostic criteria, the essential feature of ODD is a recurrent pattern of negativistic, defiant, disobedient and hostile behaviour toward authority figures that persists for at least 6 months and is characterized by the frequent occurrence of at least four of the following eight behaviours: (i) often loses temper; (ii) often argues with adults; (iii) often actively defies or refuses to comply with adults' requests or rules; (iv) often deliberately annoys people; (v) often blames others for his or her mistakes; (vi) is often touchy or easily annoyed: (vii) is often angry and resentful; and (viii) is often spiteful or vindictive.[1] ODD should be considered a disorder only when the behaviours are more frequent and intense than unaffected peers and when they cause dysfunction in social, academic or work-related situations.[2]

The International Classification of Diseases 10th Revision (ICD-10)[3] diagnostic criteria for ODD are analogous to those of the DSM-IV-TR. In the ICD-10, ODD is viewed as a mild form of conduct disorder (CD), and is characterized by negative, argumentative and defiant behaviours such as arguing with adults (table I). The ICD-10 has co-morbid diagnostic categories of 'hyperkinetic CD' (for individuals meeting diagnostic criteria for attention-deficit hyperactivity disorder [ADHD] and CD), 'depressive CD' (for individuals who meet the diagnostic criteria for CD as well as one of the mood disorders) and 'mixed disorders of conduct and emotions'.

The ICD-10 differs from the DSM-IV-TR with respect to its treatment of ODD. The ICD-10 views ODD as a mild variant of CD, i.e. ODD is considered a subtype of CD rather than a separate diagnosis.[4] The DSM-IV-TR criteria do not allow a clinical diagnosis of ODD in some cases, as evidenced in the following statement: "Oppositional behaviour is a common associated feature of mood disorders and psychotic disorders presenting in children and adolescents and should not be diagnosed separately if the symptoms occur exclusively during the course of a mood or psychotic disorder".[1] The DSM-IV-TR allows for the co-occurrence of ADHD and ODD, but does not allow for the diagnosis of ODD in adults over the age of 18 years who meet the criteria for antisocial personality disorder. CD usually presents with a poor prognosis and approximately half of the adolescents with CD may present with antisocial personality disorder in adulthood. Many patients with CD also have co-morbid sub-

stance abuse. Because of this connection between ODD and CD, ODD should be regarded seriously and should be treated effectively as early as possible.

The current diagnostic criteria for DSM-IV-TR have internal consistency and good predictive and negative predictive value. The test-retest reliability is good for parents, but poor when the child is the informant.[1] Parent-teacher agreement on ODD symptoms seem to be quite high.[2]

Negativistic and defiant behaviours are expressed by persistent stubbornness, resistance to directions and unwillingness to compromise, give in or negotiate with adults and peers. Defiance may also involve deliberate and persistent testing of limits, usually by ignoring orders, arguing and failing to accept blame for misbehaviour.[1,2]

ODD is more common in males than in females and shows a relatively high degree of stability over development.[5] It is most severe within the home environment, particularly during the childhood years, but may become equally severe in school in some children by the time they reach adolescence. A pattern of negative and coercive behaviour is often seen among other family members of the affected child. Over time, ODD is likely to be associated with low self-esteem, low frustration tolerance, temper outbursts, poor peer relations and, eventually, poor school performance. Patients with ODD may be isolated from healthier children and adolescents, may be suspended frequently from school because of behavioural problems and may experience significant friction in peer and family relationships, leading to disturbances in object relationships and a negative impact on the development of self-esteem, healthy personality and self image.[6-13]

Oppositional behaviours are common in mood disorders (e.g. dysthymic disorder, major depression or bipolar disorder). Many autistic children may show defiance and opposition, and some symptoms of ODD can also be seen in patients with organic brain disorder. DSM-IV-TR allows for the co-morbid diagnosis of ADHD, ODD and mental retardation, if the oppositional behaviour is markedly greater than is commonly observed among individuals of comparable age, sex and severity of mental retardation.[4] The presence of ODD in children and adolescents with ADHD may make treatment more complicated.

CD frequently overlaps with ODD, but according to DSM-IV-TR criteria, a diagnosis of ODD should not be made in the presence of CD or other psychiat-

Table I. International Classification of Diseases, 10th Revision (ICD-10) conduct disorders (CDs) and related diagnostic categories[3]

Category	Characteristics
Subtypes	
Oppositional defiant disorder (ODD)	A mild form of CD
Unsocialized CD	Analogous to DSM-IV-TR CD with the additional criterion of a lack of connection with peers and/or an absence of lasting friendships
Socialized CD	Analogous to DSM-IV-TR CD with the additional criterion of evidence of normal connection with peers
CD confined to the family context	CD in which the individual's disturbance occurs only in the family environment
CD unspecified	Individual meets the criteria for CD, but specific subtype cannot be established
Co-morbid diagnostic categories	
Hyperkinetic CD	Individual meets the diagnostic criteria for attention-deficit hyperactivity disorder and CD
Depressive CD	Individual meets the diagnostic criteria for CD and one of the mood disorders
Mixed disorders of conduct and emotions	Individual meets the criteria for CD and additional neurotic, stress-related or somatoform disorder according to the ICD-10 criteria
Specifiers	
Age of onset	Childhood onset: at least one CD symptom occurs before the age of 10 years Adolescent onset: CD symptoms occur after the age of 10 years
Level of severity	Mild, moderate or severe

ric disorders. Verbal aggression is more common in patients with ODD, although many patients with ODD may have mild physical aggression but do not meet the full criteria for CD. Serious, ongoing physical aggression is more commonly associated with CD. Researchers continue to address the independence of ODD and CD but recognize their interrelatedness and continuity.[6,14,15] Support for separate diagnoses rests primarily on the developmental asymmetry between ODD and CD. Research has suggested that most children who meet the criteria for CD prior to puberty will also have met the criteria for an earlier diagnosis of ODD. However, approximately 75% of children who meet the clinical criteria for a diagnosis of ODD do not progress to a diagnosis of CD during the next 3 years. Furthermore, there are a significant number of children who develop CD during adolescence without indication of a prior diagnosis of ODD.[7-13,15-17] Barkley[2] estimated that perhaps 60% of patients with ODD will develop CD and will have a high risk for substance and tobacco use.

2. General Considerations in the Pharmacological Treatment of ODD

Very few controlled studies are available on the treatment of ODD with psychoactive medications. In many studies of patients with co-morbid ADHD and ODD, ADHD is the focus of the study but patients with both ADHD and ODD have been included. The overlap of ADHD, ODD and CD has been well documented in many studies;[7-13] therefore an overlap in treatment can be expected. Thus, reports regarding effective medications in the treatment of ODD are often derived from the sub-analyses of studies designed for the treatment of ADHD.[17-54] Many of the studies of patients with ADHD and ODD have examined the use of psychostimulants. Much less is known about the utility of nonstimulant medications in treating co-morbid ADHD and ODD; however, several studies have examined the use of noradrenergic agents for these conditions.[40,55] There have been no studies examining drug therapy in patients with ODD without co-morbid disorders. Therefore, some of the improvements in ODD symptoms seen in these studies may not be directly related to the medication effects on ODD; rather, it may be possible that improvements in ODD symptoms may be related to achieving increased control of ADHD symptoms.[40]

As ODD is associated with multiple co-morbid disorders, combined drug treatment strategies may be required. Medication use in the treatment of ODD without co-morbid ADHD may be limited to patients who do not respond to psychosocial interventions and who maintain serious oppositional behaviour, defiance and aggression as part of the overall clinical picture. Many patients with ODD are suspended from school or are referred to special classes for children with serious behavioural problems. For these children, psychostimulants or atomoxetine may be effective. In patients who have failed to respond to either of these medications, TCAs, clonidine or guanfacine may be indicated.[7] For patients who have serious disruptive behaviours and who do not respond to the medications previously mentioned, the clinician should evaluate the presence or absence of mood swings and mood disorders in order to determine the need for a trial with mood regulators.

More than one-half of patients with ADHD also have ODD. Patients with co-morbid ODD and ADHD will benefit from ADHD medications, which have positive effects on ODD symptoms. Psychostimulants and atomoxetine are considered first-line medications in the treatment of ADHD, while TCAs and α_2-agonists, e.g. clonidine, can be used as second-line medications for patients with ADHD and ODD.

Longer acting psychostimulant formulations such as Adderall XR®, Concerta® and Ritalin LA® are generally more appropriate in the treatment of patients with ADHD and co-morbid ODD than short-acting formulations of psychostimultants such as methylphenidate or dexamfetamine (dextroamphetamine) because of higher remission and compliance rates, and higher teacher and parent preferences.[56] There is also less risk for medication abuse. However, a recent European review of the use of long-acting agents in hyperkinetic disorders

recommends that both long-acting and short-acting drugs should be available, with the choice determined by individual patient circumstances.[57]

Some patients exhibit ODD symptoms from early morning until bedtime. For these patients, ODD significantly interferes with the quality of life of the patient and their family. These patients may respond better to atomoxetine than psychostimulants, because atomoxetine has a longer duration of effect than all psychostimulants. Because of their sleep-suppressant effects, psychostimulants may be unsuitable for use in patients who need medication to control oppositional behaviour after dinner and at bedtime; atomoxetine may also be useful in these patients.

The dose of medication for patients with ODD and ADHD may need to be higher than that administered to patients who have ADHD without ODD.[40,55,58] Combination treatments may be indicated for highly complicated cases that do not respond well to one medication alone. Patients who have had ADHD and ODD for many years may develop major depression, particularly in adolescence. Major depression in these patients may not respond to TCAs and, therefore, these patients may benefit from the combination of psychostimulants and SSRIs. Patients with ADHD, tics or Tourette's syndrome and co-morbid ODD may also benefit from treatment with atomoxetine or clonidine because product monographs of stimulants indicate that stimulants are contraindicated in patients with tics or Tourette's syndrome.[56]

3. Drugs Used in the Treatment of ODD

3.1 Stimulants

Historically, psychostimulant medications have been first-line medications for ADHD, with reports of use dating back to 1937 for amfetamine (amphetamine) products and 1957 for methylphenidate.[4] The behavioural effects of stimulants were first described by Bradley in 1937[59] in a group of children who had mixed ADHD and other behavioural problems severe enough to warrant residential treatment. The children's behaviour improved dramatically when they received Benzedrine® (a racemic mixture of *d*- and *l*-amfetamine).[59] It was 30 years later (1967) that Conners and co-workers[60] used dexamfetamine in a double-blind study to treat a group of adolescents with behavioural problems. Regulatory approval of psychostimulant medication occurred during the 1960s.

Psychostimulants such as methylphenidate and dexamfetamine, together with their sustained-release versions, have been the standard and most common drug therapies used in the treatment of ADHD for many years. Stimulants are well tolerated and highly effective medications, with up to 75% of individuals with ADHD responding to the first stimulant selected, and a response rate of 80–90% if two different stimulants are tried consecutively.[11,56] These medications appear to be quite effective in improving symptoms of inattention, hyperactivity, impulsitivity and oppositional behaviour.[40,55]

The rating scales most commonly used to measure the effects of stimulants on ADHD, the Inattention/Overactivity With Aggression (IOWA)-Conners questionnaire,[61] the Conners' Parent Rating Scales-Revised (CPRS-R)[25] and the Conners' Teacher Rating Scales-Revised (CTRS-R),[24] have many questions relating to ODD symptoms. More recent studies with longer acting psychostimulants have utilized the Swanson, Nolan and Pelham (SNAP) questionnaire,[56] which has eight DSM-IV ODD symptoms as part of the scale. It has become clear that psychostimulants are effective in controlling both ADHD and ODD symptoms.[62]

For children with ADHD or ADHD/ODD, in the classroom setting, stimulants decrease the tendency to interrupt, fidget and finger tap, and increase on-task behaviours.[62,63] In the home setting, stimulants improve parent-child interactions, on-task behaviours and compliance. In social settings, stimulants improve peer nomination ranking of social standing and increase attention while playing baseball.[64] Many studies in children with ADHD and aggression have demonstrated the positive effects of stimulant medication in aggression control and improvement in noncompliance.[65]

The MTA (Multimodal Treatment of ADHD) study conducted by the National Institute of Mental Health was a comprehensive long-term treatment study of child psychiatric disorders.[40] As 40% of the ADHD patients also had ODD, the sub-analysis of this study also generated useful information regarding the effects of psychostimulants on ODD symptoms. For most ADHD symptoms, children in the combined or medication treatment groups showed significantly greater improvement than those given intensive psychosocial treatment alone or those treated in the community. In a direct comparison of ADHD core symptoms, combined treatment was not superior to medication management alone, and medication management was also superior to behaviour treatment alone and treatment in the community. Children with ADHD and ODD benefited more from combined therapy; for children with ADHD without ODD, both medication alone and combined treatments were equally effective. With the very high cost associated with combined treatment, it can be concluded that the presence of ODD in ADHD patients makes the cost of treatment higher, and the response rate to medication alone is not sufficient when ODD is co-morbid with ADHD. It can be postulated that early and effective interventions for behavioural problems in patients with ADHD, before the establishment of a full picture of ODD, may represent savings in healthcare delivery to these patients.[40,55,62]

The MTA study examined the moderating effects of ODD co-morbidity on ADHD treatment response, as well as the response of ODD symptoms to ADHD treatment.[55] The presence of ODD did not alter the overall pattern of findings, indicating a relative superiority of medication treatment over psychosocial or community standard interventions. ODD symptomatology, as measured by the SNAP rating scale, also showed improvement with medication treatment. Secondary analyses of the MTA study suggest that success rates for the treatment of ODD with co-morbid ADHD improve by approximately 20% when psychosocial treatment is added to medication management.[62,64]

During the last few years, there has been major progress in the development of new formulations of methylphenidate (e.g. Concerta®, Metadate CD™, Methylin® and Ritalin LA®) and amfetamine mixed salts (Adderal XR®), which have extended the duration of action of these agents. The use of long-acting medications is recommended over short-acting medications by national professional organizations such as the Canadian ADHD Resource Alliance.[56] Although initial titration with immediate-release stimulant preparations is recommended, particularly for stimulant-naive children and adolescents, conversion to one of the rapidly increasing choices of effective longer acting preparations is strongly suggested for optimal control of ADHD symptoms. Children and adolescents with ADHD and ODD require continuous symptom control and stability, and may benefit more from longer acting psychostimulants. Higher remission rates, parent and teacher preferences, improved compliance and better maintenance of privacy, particularly for adolescents, are some of the main reasons leading to the recommendations of preference of longer acting medications proposed by national ADHD associations.[56] A recent review of studies comparing the long-acting methylphenidate formulation (Concerta®) with the immediate-release methylphenidate formulation (Ritalin®) has provided evidence that children with ADHD who took equal amounts of methylphenidate demonstrated much higher rates of remission of ADHD symptoms with Concerta®.[66] Symptoms of ODD also responded better to Concerta® than to Ritalin®.[66]

Effect sizes for changes in behaviour and attention in short-term trials with psychostimulants range from 0.8 to 1.0, which is quite a significant effect.[67] Double-blind, placebo-controlled studies report moderate adverse effects in 4–10% of children treated. Delay in sleep onset, reduced appetite, stomach ache, headache and jitteriness are the most frequently cited adverse effects of methylphenidate.[68] A review of the meta-analytic studies and recent guidelines on the use of psychostimulants support the use of these medications for oppositional and aggressive behaviour in the absence of

ADHD.[56,57,65] Short-term trials of stimulants (most often ≤3 months in duration) have reported robust efficacy of methylphenidate, dexamfetamine and pemoline, with equal efficacy among stimulants.[59,60,67,69,70] Short-term trials have reported improvements in the most common ADHD symptoms, and improvements in behavioural symptoms, including overt aggression, as long as medication is taken consistently.[67]

A recent meta-analysis of all studies dealing with aggressive behaviour in children and adolescents concluded that stimulants exerted a medium to large effect (effect size = 0.78) and risperidone exerted a strong effect size (0.9). Limited studies with atomoxetine did not show a strong positive effect (effect size = 0.18) in controlling aggression.[70] The effect sizes in treating aggressive behaviour were moderate for lithium (0.4) and guanfacine (0.4), and small for antidepressants (0.3). As most patients with ODD have aggressive behaviours, the effect size on aggressive behaviour should be considered when choosing medication for treating this disorder.

3.2 Atomoxetine

Atomoxetine is a specific noradrenaline (norepinephrine) transporter inhibitor. It is a nonstimulant medication, which has received US FDA approval, and is not classified as a controlled substance. Short-term, placebo-controlled studies[58,71,72] and long-term use indicate that atomoxetine may be a reliable and well tolerated alternative to stimulant drugs in the treatment of ADHD inattentive, hyperactive-impulsive and combined types. The studies used Conners' rating scales and DSM-IV symptom-based, clinician-completed rating scales.[25,73,74] Patients maintained treatment gains during the long-term study,[72] and the adverse effect profile seemed to be acceptable, with no serious problems. Increased risk of suicidal ideation, as well as rare serious adverse effects on the liver and heart have been reported with atomoxetine.[72]

One of the major advantages of atomoxetine, compared with other ADHD medications, is its long duration effect, which alleviates behavioural problems and inattention early in the mornings and late in the evenings. Results of an 8-week, randomized, placebo-controlled trial of once-daily atomoxetine in a total of 197 children with ADHD (aged 6–12 years) revealed that medication efficacy on the home behaviours of children persists into the evening and the following early morning.[75] Atomoxetine seems to be effective for as long as 24 hours following a single morning administration; it also helps to control anxiety symptoms and tics.[76] Atomoxetine was found to be effective in the treatment of ODD and ADHD co-morbidities.[77] New research findings with atomoxetine in treatment-resistant patients with ADHD has established the functional use of plasma concentrations to guide atomoxetine doses.[71]

Newcorn et al.[58] reported on atomoxetine treatment in children and adolescents with ADHD and co-morbid ODD. Of 297 children and adolescents randomly assigned to receive medication, 293 had complete information regarding the presence or absence of lifetime ODD. Of these, 115 (39.3%) met DSM-IV-TR criteria for ODD. Atomoxetine 1.8 mg/kg/day (but not 1.2 mg/kg/day) was superior to placebo in reducing symptoms of ADHD among youths with ADHD and ODD, as assessed by the ADHD Rating Scale IV-Parent Version. Changes in ADHD and oppositional symptoms were associated with improvements in broader functioning. Effect-size measurements indicated medium to large effects on oppositional symptoms in the ODD group, comparable to those associated with stimulant treatment of aggression-related behaviours in ADHD. The effect sizes for changes in oppositional behaviour were also consistent with those obtained in this treatment group on measures of ADHD symptoms. Youths with and without ODD differed in their dose-response characteristics, with patients without ODD showing a maximal response at 1.2 mg/kg/day and patients with ODD showing a greater response at 1.8 mg/kg/day.

Additional research is required to establish atomoxetine as a treatment for ODD and to evaluate whether higher doses are required when ODD co-morbidity is present.

3.3 Antidepressants

The pharmacokinetics of and treatment responses to TCAs are different in children than in adolescents or adults. Prepubertal children are prone to rapid dramatic swings in blood concentrations (from toxic to ineffective levels) and should be given divided doses to produce more stable concentrations.[78,79] The short half-life of TCAs in prepubertal children can produce daily withdrawal symptoms if medication is administered only once daily. TCAs should be tapered over a 2- to 3-week period. Five cases of unexplained sudden death have occurred during treatment with desipramine, three of which were following exercise in prepubertal children.[80] A causal relationship between the medication and the deaths has not been established.

TCAs such as imipramine or desipramine, which have been effective in treating ADHD,[78,79] can be considered; however, patients with associated anxiety or mood disorders (major depression or dysthymic disorders) may benefit from the newer antidepressants, such as the SSRIs. The specific impact on ODD symptoms in these clinical conditions is not well established.

A trial with TCAs may be considered for patients with ADHD and ODD who do not respond to psychostimulants and atomoxetine, or who have developed tics and/or Tourette's syndrome while taking psychostimulants. A starting dosage of 10 mg two or three times daily, with a gradual dosage increase up to a maximum of 2–3 mg/kg/day under careful cardiac monitoring with ECG, can be considered.[11,56]

Bupropion, a mixed dopaminergic/noradrenergic agonist, has been shown to be effective in treating children with ADHD.[11,56] However, most studies of bupropion in ADHD are limited by their small sample sizes and focus on symptoms of aggression, not ODD. Bupropion has a favourable adverse effect profile, with low cardiotoxicity. A newer slow-release formulation of bupropion is a potential candidate for the treatment of co-morbid ADHD and alcohol/substance use disorder, for several reasons. First, its status as an indirect dopamine agonist and enhancer of noradrenaline (norepinephrine) bioavailability is positive.[69] Having both noradrenergic and dopaminergic mechanisms may make it a useful agent for the treatment of ADHD. Bupropion may decrease hyperactivity and aggression, and perhaps improve cognitive performance in children with ADHD and CD.[81-83] One double-blind, cross-over study found the efficacy of bupropion to be statistically equal to methylphenidate in children and adolescents with ADHD.[83] Although similar to other nonstimulant medications, the behavioural effects of bupropion may be greater than the cognitive effects. Bupropion is administered in two or three doses, beginning with a low dose (37.5 or 50 mg) twice daily, with titration over 2 weeks to a usual maximum of 250 mg/day in children and 300–400 mg/day in adolescents. The most serious potential adverse effect with this drug is a decrease in the seizure threshold, seen most frequently in patients with eating disorders or at dosages >450 mg/day.

There have been some positive reports about the effects of the serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine on ADHD symptoms in adults,[84,85] but there are as yet no controlled studies in children that have a major focus on not only ADHD symptoms but also the common co-morbid disorder, ODD.

3.4 α_2-Agonists

The α_2-agonists, clonidine and guanfacine, may be considered as second-line medications for the treatment of ADHD.

Studies with clonidine in patients with ADHD have reported treatment effectiveness.[86,87] A pilot study of methylphenidate, clonidine or the combination of these agents in ADHD co-morbid with aggressive ODD or CD showed positive effects of clonidine on behavioural problems, including ODD symptoms.[86] In a meta-analysis of 11 randomized, double-blind, controlled studies from 1980 to 1999, clonidine demonstrated a moderate effect size of 0.58 on symptoms of ADHD alone and with co-morbid CD, developmental delay and tic disorders.[88] Results from an open-label pilot study of clonidine (maximum optimal dosage 0.4 mg/day) in

aggressive children indicate that this medication may be associated with reductions in aggression and have only mild adverse effects.[89]

The following patient groups may be considered for a trial with clonidine or guanfacine: patients with ADHD and CD, patients with ADHD and severe ODD, ADHD patients with tics or Tourette's syndrome, and patients with ADHD and ODD who do not respond to treatment with psychostimulants and atomoxetine. Clonidine and guanfacine remain useful in selected ADHD patients who respond better to these medications than other drugs, but the magnitude of efficacy and/or the tolerability of these medications have limited their use. Well controlled studies with larger sample sizes are required to further define their role. Clonidine and guanfacine have not been approved by the FDA for the treatment of ADHD and ODD.

3.5 Mood Regulators

The most commonly used and studied mood regulators for aggression and mood dysregulation are lithium, carbamazepine and valproate (valproic acid).

Two placebo-controlled studies demonstrated that, at therapeutic concentrations, lithium was efficacious and well tolerated for the short-term treatment of aggressive inpatient children and adolescents with CD.[90,91] A third study found no differences between lithium and placebo in a small sample of inpatient adolescents with CD; however, lithium was administered for only 2 weeks.[92] A controlled trial comparing lithium, haloperidol and placebo showed that both lithium and haloperidol were efficacious for the treatment of inpatient aggressive children with CD, but lithium was better tolerated than haloperidol.[93]

A small pilot study[94] of carbamazepine showed effectiveness in reducing aggressive behaviour in hospitalized adolescents with aggressive behaviour and CD. However, when administered in dosages of 400–800 mg/day in a small, double-blind, placebo-controlled study of 22 prepubertal children, carbamazepine at therapeutic concentrations was not significantly better than placebo for the control of aggressive behaviour.[95]

There have been no studies published to date regarding the effectiveness and tolerability of lamotrigine in the treatment of ODD.

For children and adolescents with ADHD and bipolar disorders, either mood regulators or risperidone or the combination of these agents may be considered.[79] When bipolar disorder symptoms are under control, patients with ADHD may require the careful addition of psychostimulants or atomoxetine. Clinicians should closely monitor patients with bipolar disorder and ODD to ensure that psychostimulant use does not provoke a manic or hypomanic episode. In summary, highly complicated cases of bipolar disorder, ADHD and CD may require close consultation with a child and adolescent psychiatrist and a highly specialized clinic to support general practitioners and paediatricians in treating these patients.[56]

In patients with mood disorders, ODD and ADHD, mood regulators may have a role in treatment. ODD symptoms may improve with the effective treatment of the mood disorder and the ADHD.

3.6 Antipsychotics

One of the most significant reasons for reviewing the use of antipsychotic medications in the treatment of ODD is the close links between ODD and aggressive behaviour, and ODD and CD. Methylphenidate has been found to be significantly more effective than placebo, and well tolerated in the treatment of a large group of outpatients (children and adolescents) with CD. Most of these patients also had ODD.[96] The adverse effect profile of psychostimulants may make them preferable to antipsychotics for treating these patients. Patients who do not respond to trials with psychostimulants may still present a danger to themselves and others because of verbal and physical aggression. These symptoms may require a trial with newer generation atypical antipsychotics.

Atypical antipsychotics are used to treat aggressive and oppositional behaviours that do not respond to other medications. Risperidone is the most studied medication in this category, with placebo-con-

trolled, multicentre trials in patients with CD and ODD, with or without ADHD. Risperidone was reported to be superior to placebo and well tolerated in the short-term treatment of a small group of outpatient children and adolescents with ODD and CD.[97]

The effectiveness of risperidone has also been demonstrated in children with ODD and CD with a sub-average IQ, autism or other pervasive developmental disorders, and other disruptive behaviour disorders (DBDs), with or without ADHD.[98,99] A randomized controlled trial of risperidone in the treatment of aggression in hospitalized adolescents with sub-average cognitive abilities showed effectiveness in oppositional behaviour and aggression.[99] A double-blind, placebo-controlled, multisite study established the role of risperidone in controlling oppositional, defiant, aggressive and self-injurious behaviour of children with autism and other pervasive developmental disorders.[100] Adverse effects, including sedation with secondary cognitive effects, hypotension, extrapyramidal symptoms, tardive dyskinesias and obesity, should be weighed up against the possible benefits of pharmacological treatment.

A randomized, double-blind, placebo-controlled study was conducted to determine whether risperidone was effective in reducing symptoms of disruptive behaviours (such as aggression, impulsivity, defiance of authority figures and property destruction) associated with ODD, CD and DBDs not otherwise specified (NOS) in children with a sub-average IQ.[101] The trial consisted of a 1-week, single-blind, placebo run-in period and was followed by a 6-week treatment phase. 110 children (aged 5–12 years, inclusive) with an IQ of 36–84, a DBD and a score of ≥24 on the Conduct Problem subscale of the Nisonger Child Behavior Rating Form (NCBRF)[102] were involved. Eighty percent of patients had co-morbid ADHD. The risperidone dosages ranged from 0.02 to 0.06 mg/kg/day. The most common adverse effects included somnolence, headache, appetite and weight increase. Risperidone appeared to be an adequately tolerated and effective treatment in children with sub-average IQ and severe DBDs such as aggression and destructive behaviour.[101]

A long-term study also investigated the safety and efficacy of risperidone in DBDs in children with sub-average IQ.[103] DBDs were defined as ODD, DBD-NOS and CD, as per DSM-IV diagnostic criteria. This 48-week, open-label extension study of risperidone was conducted in 77 children diagnosed with a DBD and either borderline intellectual function, or mild or moderate mental retardation who had participated in the above outlined study.[101] Participants received an oral solution of risperidone administered at a once-daily dose of between 0.02 and 0.06 mg/kg for a maximum of 54 weeks.[103] Somnolence, headache and weight gain were the most common adverse effects. The degree of sedation was mild and transitional, and was not associated with cognitive deterioration. Approximately half of the 8.5 kg average weight gain was attributable to normal growth. At the study endpoint, the mean prolactin level was statistically significantly greater than baseline in male participants only, but was still <20 ng/mL, which is within the normal range. Twenty participants experienced mild or moderate extrapyramidal symptoms, although none withdrew for this reason. The authors concluded that risperidone was effective and safe in controlling DBDs in children between the ages of 5 and 12 years, with or without ADHD.[103]

Similar findings on the effects of risperidone in severe ODD and CD with aggression in children with sub-average intelligence with or without ADHD have been reported in an almost mirror-image US multicentre study.[104] The effects of risperidone in the presence/absence of psychostimulant medicine in children with ADHD, other DBDs and sub-average IQ were reported[105] as a sub-analysis of the study by Snyder et al.,[101] with a specific focus on the anti-ADHD effects of risperidone. The analysis included 155 children with mental retardation or borderline intellectual functioning who presented with either CD or ODD.[105] All children had serious aggressive behaviours. The children were divided into four subgroups (with 35–43 patients in each) – placebo only, psychostim-

ulant only, placebo plus risperidone, or risperidone plus psychostimulant. Within each randomized treatment group, actual weight gain was comparable, regardless of concomitant stimulant use. The addition of risperidone to a psychostimulant resulted in significantly better control of hyperactivity ($p < 0.001$) than was achieved with stimulant treatment alone, without causing an increase in adverse events. The study concluded that, in this type of patient population, risperidone was effective in controlling ADHD, aggression, and CD or ODD symptoms.[105]

For patients with severe aggression and ODD or CD with or without ADHD (who do not respond to psychostimulants and atomoxetine), the recommended starting dosage of risperidone is 0.02 mg/kg/day. The dosage can be increased gradually up to 0.06 mg/kg/day.[7,101,103-105] The use of risperidone, with or without sedating medications, for the management of adult patients with variable agitation and aggression in emergency settings has also been reported.[106,107]

The maintenance of positive effects, with improvements in weight control and decreases in prolactin levels after the initial few months of risperidone use, has been reported.[108] Concerns regarding initial weight gain and prolactin increases are diminishing.

3.7 Medication Combinations

3.7.1 Stimulants and Clonidine

One of the most common medication combinations currently used in the treatment of ADHD is a stimulant taken with clonidine. Anecdotal clinical experience and, more recently, controlled studies,[109,110] support the usefulness of this combination, particularly in children with severe ADHD with aggressive behaviour, and for children who are not well managed on a stimulant alone. The combination of clonidine and psychostimulants may allow for a lower dose of stimulant medication.[110]

Some clinicians add clonidine before bedtime to cancel out the sleep-suppressant effects of stimulants.[111] The addition of clonidine to psychostimulants may improve the ability to fall asleep, whether insomnia is due to ADHD over-arousal, oppositional refusal, or stimulant effect or rebound.[112]

However, questions have been raised about the safety of the combination of clonidine and stimulants.[111] Four deaths have been reported to the FDA of children who at one time had been taking both methylphenidate and clonidine; the evidence linking these medications to the deaths is tenuous at this time.[109] Pending additional data, caution is advised when treating children with cardiac or cardiovascular disease, when combining clonidine with additional medications, or if the dosage of medication is different from product monographs or treatment guidelines. Caution is also advised when administering methylphenidate monotherapy to children, adolescents and adults with possible cardiac problems. Paediatric cardiology consultation is recommended for questionable cardiac problems.

Clonidine or guanfacine are considered first-line agents in tic disorders and Tourette's syndrome disorder because of their modest efficacy and relatively benign adverse effect profile compared with antipsychotic agents. A 16-week, randomized, double-blind, multicentre trial conducted in 136 children with ADHD and a chronic tic disorder evaluated clonidine, methylphenidate, and combined treatment with clonidine and methylphenidate compared with placebo. Efficacy was reported for clonidine and methylphenidate monotherapy and the greatest benefit occurred with combined treatment with clonidine and methylphenidate ($p < 0.0001$ vs placebo).[113]

3.7.2 Stimulants and Antidepressants

The combination of methylphenidate and imipramine has been associated with a syndrome of confusion, affective liability, marked aggression and severe agitation.[114] Methylphenidate may interfere with the hepatic metabolism of imipramine, resulting in a longer half-life and elevated blood concentrations.[115]

Gammon and Brown[116] combined fluoxetine and methylphenidate for the treatment of ADHD and co-morbid depressive disorder, and reported the effectiveness and safety of this combination. The

sample size was small and it is hoped that these results will be replicated with a larger study.

3.7.3 Stimulants and Antipsychotics

In three double-blind, placebo-controlled studies of children with ODD and/or CD (with or without ADHD) and sub-average IQ, the combination of dexamfetamine and risperidone has been found to be effective and well tolerated.[101,103,105]

4. Treatment Algorithm for ODD

The following suggested algorithmic approach for the treatment of ODD was developed through the integration of the evidence-based literature reviewed in sections 1–3 and the clinical experience of the author. This proposed algorithmic approach is included in this publication to initiate discussion and debate, since no medication algorithm for ODD currently exists in the literature.

4.1 ODD Alone

Step 1: A comprehensive evaluation is required to establish the presence of co-morbid disorders and/or to rule out these disorders: use a general psychopathology screening and rating scale[23-26] or a structured interview.

Step 2: For a single diagnosis of ODD, in the absence of other psychiatric disorders, psychosocial interventions should be attempted first.

Step 3: If psychosocial interventions do not provide improvement within the first 2–3 months, either psychostimulants (which have proven effectiveness in the treatment of ODD) or atomoxetine (which has shown effectiveness in the treatment of ODD) may be tried. If the patient does not respond to the first medication, a second medication from a different class can be tried. If aggression is part of the clinical picture, the first two trials should be either a methylphenidate- or amfetamine-based medication. For example, if a methylphenidate-based medication is tried and the patient does not respond, the next trial can be an amfetamine-based psychostimulant or atomoxetine. Since patients with ODD do not comply well with taking medication, long-acting medications are recommended in order to increase compliance, which can be monitored by parents in the mornings. If the first two trials were with psychostimulants, and an adequate response is not achieved, then a trial with atomoxetine is indicated. Children and adolescents with serious behavioural issues who do not respond to psychosocial interventions followed by psychostimulants or atomoxetine may be considered for a trial with risperidone.

4.2 ODD + ADHD, Without Anxiety, Mood or Tic Disorders

For most patients with ODD and co-morbid ADHD, aggression is part of the clinical picture; either methylphenidate- or amfetamine-based psychostimulants should be tried first (see step 3 as detailed in section 4.1).

4.3 ODD + ADHD + Either Tic and/or Anxiety Disorders

Atomoxetine can be tried first. For patients who have not responded to a trial with atomoxetine, either a methylphenidate- or amfetamine-based trial may follow. For patients who have not responded to any of these drugs, a trial with imipramine can be undertaken. For patients with ADHD + ODD + tic disorders without anxiety disorders, clonidine or guanfacine may be tried. Patients with severe aggressive behaviours who do not respond to psychostimulants and who continue to be a threat to their own safety or the safety of others, may require the use of risperidone alone or in combination with psychostimulants until the aggressive behaviours are under control.

4.4 ODD + Mood Disorders + ADHD

For patients with severe mood disorders, an effective antidepressant (possibly an SSRI) can be initiated. After the clearance of major mood disorder symptoms, the treatment of the remaining ODD and ADHD symptoms may require additional medications. The safety of combining atomoxetine with antidepressants has not yet been established; however, the safety of the combination of SSRIs or TCAs with psychostimulants has been well estab-

lished.[78,79] A methylphenidate- or amfetamine-based psychostimulant can therefore be combined with antidepressant medication. For adults with ODD and mood disorders, imipramine or desipramine can also be considered, as TCAs are effective in treating ADHD symptoms. In children and adolescents, TCAs were not found to be effective in treating major depression.[78,79]

4.5 Other Multiple Co-Morbidities

For patients whose multiple co-morbid conditions associated with ODD do not fit into any of the combinations described above, an urgent consultation with a clinic or clinician specializing in the treatment of ODD is advised. Children and adolescents with ODD (with or without ADHD) who have depression and suicidal thoughts have a high risk for self-injurious behaviour and suicide. An urgent child and adolescent psychiatric consultation may support the primary care physicians dealing with these complicated patients.[79]

Over the last few years American, Canadian and European reviews and position papers, as well as books, have been published that have included guidelines for the use of medications in the treatment of ADHD and ODD.[56,117-119] These review papers and practice parameters have recommended a 'multimodal and extensive' approach involving individual and family therapeutic, psychosocial approaches and medication in the treatment of ODD.

5. Conclusion

ODD is a common disorder in childhood and adolescence, in both clinical and nonclinical samples. Simple ODD without other co-morbid disorders is a serious clinical syndrome, often leading to isolation and socialization difficulties. In some cases, it can lead to more serious psychopathology, such as CD and substance abuse.

The presence of ODD increases the risk of having co-morbid ADHD and CD. Official diagnostic classification systems and evidence-based studies of ODD clearly establish the links between ODD, ADHD and CD. There is significant support in the research to indicate that some patients with ODD develop CD, and ODD seems to be a milder version of CD. Hence, ODD should be identified and treated as early and as effectively as possible.

Most of our knowledge regarding the pharmacotherapy of ODD is based on co-morbidity studies of ODD with ADHD and/or CD. It is unfortunate that there is a lack of strong, evidence-based studies regarding the treatment of simple ODD, particularly in community samples. It is hoped that future research will shed light on this area as there are many ODD patients with severe and long-standing symptoms who do not respond to psychosocial interventions and/or are not motivated to pursue such treatment alternatives.

A few controlled studies of patients with co-morbid ODD and ADHD indicate that ADHD medications are also effective in treating ODD. The doses of medication may need to be higher when ODD is associated with ADHD. It is hoped that research in the near future will focus on ODD-specific research with patients in community samples. As the MTA study[55] demonstrated, the presence of ODD in children and adolescents with ADHD may require psychosocial and psychoeducational interventions added to medication treatment.

Future studies on the comparative effectiveness of psychosocial and medication approaches and their combination in the management of ODD with or without its common co-morbidities may clarify the most effective treatment alternatives for ODD. This may empower those in the health and mental health systems to treat patients with ODD, and may aid in the prevention of more serious psychopathologies, including CD.

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