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Research in Developmental Disabilities 27 (2006) 309–336

Research
in
Developmental
Disabilities

Guidelines for the use of clozapine in individuals with developmental disabilities

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Received 7 February 2005; received in revised form 5 May 2005; accepted 9 May 2005

Abstract

Clozapine is the most effective antipsychotic medication currently in use, but there has been a paucity of well-controlled research on its efficacy with people with developmental disabilities. We present a set of guidelines to ensure proper utilization of clozapine in individuals with developmental disabilities, because it can offer them therapeutic advantages similar to those observed in people with schizophrenia. We provide recommendations regarding the use of clozapine that are based on three main sources: literature and published professional practice guidelines regarding the use of clozapine in individuals who do not have developmental disabilities, the limited literature on the use of clozapine in individuals who have developmental disabilities, and our own clinical experience. The first part of the guidelines contains an overview of necessary practical knowledge regarding side effects, dose and blood level considerations, and interactions with other medications, diet and tobacco smoking. In the second part, we offer procedures for selecting individuals for clozapine therapy based on proper indications and contraindications for treatment. We also include requirements regarding informed consent, dosage and special laboratory and clinical monitoring.

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Keywords: Clozapine; Clozapine guidelines; Individuals with developmental disabilities; Antipsychotic medication

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1. Introduction

Clozapine is an atypical or new generation antipsychotic (NGA) medication currently manufactured by Novartis Pharmaceutical Corporation and marketed under the trade name of Clozaril. It is indicated for use in individuals with schizophrenia who are either resistant or intolerant to other antipsychotic drugs (Baldessarini & Frankenburg, 1991; Kane, Honigfeld, Singer, & Meltzer, 1988). The efficacy of clozapine in people with schizophrenia has been proven to be superior to that of the conventional or first-generation antipsychotic (FGA) agents according to individual studies (Kane et al., 1988; Singer & Law, 1974) and a meta-analytic review (Wahlbeck, Cheine, Essalieu, & Adams, 1999). Clozapine may also be superior to other NGA agents (Conley & Buchanan, 1997). Both positive and negative symptoms appear to improve when treated with clozapine (Tandon et al., 1993). Clozapine can help achieve a treatment response characterized by not only symptom reduction but also improvement in certain aspects of cognitive functioning, social functioning and quality of life, decreased need for hospitalization, and enhanced compliance with treatment (Grace et al., 1996; Meltzer, 1992; Meltzer, Burnett, Bastani, & Ramirez, 1990). Furthermore, treatment with clozapine significantly reduces suicidal behavior among schizophrenic individuals (Barclay, 2003; Meltzer et al., 2003).

Clozapine has been also shown to be effective in individuals with schizoaffective and psychotic mood disorders (McElroy, 1991; Zarate, Tohen, & Baldessarini, 1995), non-psychotic rapid cycling bipolar disorder (Suppes, Phillips, & Judd, 1994), and Parkinson's disease with drug-induced and other concomitant psychosis (Friedman & Lannon, 1989; TPSG, 1999). Furthermore, clozapine has been demonstrated to be effective in individuals with brain injury (Michals, Crismon, Roberts, & Childs, 1993), co-morbid schizophrenia and substance use disorder (Green, Zimmet, Strous, & Schildkraut, 1999), and severe borderline personality disorder with aggression and self-abusive behavior (Benedetti, Sforzini, Colombo, Maffei, & Smeraldi, 1998; Chengappa, Ebeling, Kang, Levine, & Parepally, 1999). Although studies are limited, clozapine appears to be the best treatment for polydipsia associated with severe mental illness (Canuso & Goldman, 1999; Verghese, de Leon, & Josiassen, 1996). While polydipsia is typically associated with schizophrenia, it is also reported in 5% of hospitalized individuals with mental retardation (Bremner & Regan, 1991; Deb, Bramble, Drybala, Boyle, & Bruce, 1994; Hayfron-Benjamin, Peters, & Woodhouse, 1996). In individuals with schizophrenia, the polydipsia response to clozapine appears to be independent from the antipsychotic response (Verghese et al., 1996).

The use of clozapine among individuals with developmental disabilities is becoming increasingly accepted due to efficacy and safety profiles similar to those reported among individuals without developmental disabilities. Since the early 1990s, several retrospective analyses (Antonacci & de Groot, 2000; Buzan, Dubovsky, Firestone, & Dal Pozzo, 1998), case reports/series (Cohen & Underwood, 1994; Gobbi, 2001; Pary, 1994; Sajatovic, Ramirez, Kenny, & Meltzer, 1994), and single blind studies (Hammock, Levine, & Schroeder, 2001) have shown that relatively low doses of clozapine are effective in improving psychotic symptoms, self-injurious behavior, aggression, property destruction and stereotyped behavior. A few double-blind placebo-controlled studies have confirmed the efficacy of clozapine in this population (Hammock, Schroeder, & Levine, 1995;

Schroeder et al., 1995). These benefits were observed in individuals with the full range of mental retardation and without evidence of increased risk of side effects at doses under 600 mg/day or a decline in cognitive processes. In these studies, clozapine was generally effective and well tolerated by individuals who had failed behavioral and other pharmacological treatments. In most of the studies, the minimum effective dose was 200 mg/day. The benefits were reported both in individuals who met diagnostic criteria for schizophrenia, schizoaffective or bipolar manic disorder and in those who did not meet criteria for these Axis I diagnoses (Buzan et al., 1998). Some reports suggest that clozapine is more effective than other NGA agents (e.g., risperidone) as evidenced by progressive improvement in symptoms during the length of the trial (Gobbi, 2001). In addition, case reports suggest that individuals with autism with complicated polydipsia may respond to a low dose of clozapine (<300 mg/day) (de Leon, 2003a).

2. Side effects

2.1. Agranulocytosis

Agranulocytosis, defined as an absolute neutrophil count of less than 500 mm^{-3} , is the most serious side effect of clozapine, and the negative perception of this risk has limited clozapine's use. Clinical testing of clozapine prior to domestic marketing suggests that agranulocytosis may occur at a cumulative incidence of 1.3% at 1 year (NPC, 2003). If caught early, agranulocytosis is usually reversible with discontinuation of clozapine treatment. Some cases of agranulocytosis have progressed in spite of detection and discontinuation of clozapine. As of August 21, 1997, under a weekly blood monitoring system, 585 cases of agranulocytosis have been detected in the United States out of 150,409 individuals receiving clozapine; 19 were fatal (NPC, 2003). Data from the Clozaril National Registry (CNR) indicates a cumulative rate of 0.9% (Alvir, Lieberman, Safferman, Schwimmer, & Schaff, 1993; NPC, 2004). The risk of agranulocytosis seems to peak by the third month of therapy and declines significantly after the sixth month, but never reaches zero (Alvir et al., 1993). This finding led to recommendation that the white blood cell (WBC) count monitoring be decreased from weekly to biweekly after 6 months of clozapine therapy.

Agranulocytosis is potentially fatal and considered a medical emergency. The risk of agranulocytosis appears to increase with age, is higher in women than in men and particularly high in Ashkenazi Jews (Lieberman et al., 1990). Safeguards to manage the risk of agranulocytosis, such as registration through CNR and the requirement for weekly drug monitoring during the first 6 months of therapy have resulted in lowering the incidence of this condition.

2.2. Myocarditis and cardiomyopathy

Myocarditis is a rare and potentially fatal adverse effect of clozapine therapy (Kilian, Kerr, Lawrence, & Celermajer, 1999). Based on post-marketing surveillance data, which revealed 30 reports of myocarditis with 17 fatalities in 205,493 U.S. patients, the box

warning regarding the risk of clozapine-associated myocarditis has been strengthened (NPC, 2002). The risk may be highest during the first month of therapy, but it continues as long as the drug is administered (NPC, 2002; Wooltorton, 2002).

Signs of myocarditis include tachycardia, unexplained fatigue, dyspnea, fever, chest pain, palpitations, other signs or symptoms of heart failure or EKG findings such as ST-T wave abnormalities or arrhythmias. Any individual in whom myocarditis is suspected should be admitted to the hospital for observation and treatment with corticosteroids, if necessary. Individuals with clozapine-induced myocarditis should not be rechallenged with clozapine.

Clozapine treatment may be associated with the development of cardiomyopathy. The risk of cardiomyopathy may be at least five times greater in individuals receiving clozapine therapy than that in the general population (Kilian et al., 1999).

2.3. Seizures

Clozapine-associated seizures are estimated to occur at a cumulative incidence of approximately 5% (NPC, 2003) and appear to be related to dose and rate of titration (Iqbal et al., 2003; Miller, 2000; NPC, 2003). The risk of seizures should be carefully monitored in individuals with developmental disabilities, especially in those with severe to profound range of mental retardation. Although clozapine therapy increases the risk of seizures, none of the studies that we reviewed in this group of individuals has revealed an increased risk in this population. However, the dose of clozapine used in these studies was relatively low. The most common type of clozapine-associated seizures is generalized tonic-clonic seizures. Myoclonic seizures without loss of consciousness or with progression to tonic-clonic seizures may also occur. Absence seizures are rare. If an individual taking clozapine develops an isolated seizure, this may not be a reason for discontinuation of treatment (Iqbal et al., 2003). However, if seizures persist, a neurology consultation should be obtained.

2.4. Metabolic complications

Weight gain is well-documented in clozapine therapy. Many individuals gain more than 20% of their initial body weight during the first year of treatment (Meyer, 2001). Some studies have reported an average weight gain of 5.3–6.3 kg (11.8–14.0 lb). Possible mechanisms for the weight gain include antagonism of 5-HT_{2c} and H₁ receptors (Wirshing et al., 2002). Weight gain appears to be linked to clinical improvement, and the risk seems to increase with the duration of treatment, especially during the first 4 years of treatment (Henderson et al., 2000; Miller, 2000). Weight gain is best managed with dietary interventions (e.g., nutritional consultation and dietary regimens) and exercise.

A number of recent studies have highlighted the increased risk of hyperglycemia, lipid abnormalities and diabetes mellitus (type 2) in individuals receiving clozapine and other NGA medications (Allison et al., 1999; Gianfrancesco, Grogg, Mahmoud, Wang, & Nasrallah, 2002; Henderson et al., 2000; Wirshing et al., 2002). The Food and Drug Administration (FDA) has issued a class labelling change regarding the risks of hyperglycemia and diabetes mellitus in association with NGA medications (FDA, 2003).

It has not been determined if changes in glucose and lipid metabolism are linked to weight gain (Wirshing et al., 2002).

Epidemiological studies have suggested an increased risk of hyperglycemia-related adverse events in individuals treated with NGA. However, the precise risk estimates are not available (FDA, 2003). Reports indicate a relatively high rate of new-onset diabetes during treatment with clozapine ranging from 12 to 36.6% of those on clozapine therapy (Hagg et al., 1998; Henderson et al., 2000). Confounding factors for a higher rate of new-onset diabetes include a diagnosis of schizophrenia, lack of physical activity, dietary intake and an African American race. Despite these factors, clozapine therapy by itself appears to carry an increased risk for diabetes mellitus. Mechanisms other than obesity may be involved in clozapine-associated type 2 diabetes and include suppression of insulin release, insulin resistance, or impairment of glucose utilization (Henderson et al., 2000). If diabetes and/or hyperlipidemia develop, a medical consultation is needed. Early detection of diabetes, control with diet, and individual and family education are important.

Clozapine therapy has been associated with elevated triglyceride levels which is an independent risk for coronary atherosclerosis (Ghaeli & Dufresne, 1996; Henderson et al., 2000; Meyer, 2001; Wirshing et al., 2002). The mechanisms of clozapine-associated hyperlipidemia are largely unknown.

2.5. Orthostatic changes and tachycardia

Clozapine's propensity to cause orthostatic changes can be explained by its alpha receptor antagonistic properties. Orthostatic hypotension is usually transient and occurs during initial treatment. Tolerance develops in most cases. The prevalence and severity are related to the pace and magnitude of dose titration (Miller, 2000).

Tachycardia is a common side effect of clozapine treatment, occurring in about 25% of cases (Miller, 2000). It may be associated with the hypotensive effect, but the main cause is the anticholinergic effects of clozapine and its elevation of plasma norepinephrine (Miller, 2000). Tachycardia may be transient and related to dose titration or persistent. In some cases, it may be indicative of myocarditis.

Orthostatic changes and tachycardia can be avoided by careful monitoring and delaying titration to allow the individual to develop tolerance. Rising slowly from the sitting or the lying position and increasing fluid and salt intake (if not contraindicated) are advised. Support stockings and tilting the head of the bed at night may be needed. Pharmacological management with fludrocortisone or ephedrine may be indicated for some individuals. In most cases, however, the changes disappear over time.

2.6. Fever

The presence of fever and/or infection may be indicative of the presence of agranulocytosis. However, most cases of fever in individuals on clozapine therapy are merely unrelated infections. Any infections must be treated promptly. If the individual has fever and no cause is found, it may be a clozapine-induced benign hyperthermia that occurs in up to 5% of individuals, usually within the first 3 weeks of treatment. It typically

involves minor increases of 1 or 2 F which disappears with the continuation of treatment (Safferman, Lieberman, Kane, Szymanski, & Kinon, 1991).

2.7. Sedation

Sedation is the most common side effect of clozapine treatment, occurring in 39% of cases (Miller, 2000; NPC, 2003). The condition is usually mild, tends to occur during the initial phase of treatment, and is transient (Miller, 2000). Some individuals develop some tolerance to sedation, but for others, sedation becomes a persistent side effect. The risk of sedation is decreased by giving higher doses at night, slower titration, or dose reduction. In severe cases, pharmacological management with stimulants should be considered, but it should be done with caution because of the risk of worsening psychosis (Iqbal et al., 2003).

2.8. Constipation

Clozapine has strong anticholinergic effects and, thus, can cause severe constipation. A high fiber diet, adequate fluid intake and exercise minimize the risk of constipation. Fiber supplements, stool softeners, laxatives, stimulant cathartics or enemas may be needed depending on the severity of the condition.

2.9. Hypersalivation

Unlike most antimuscarinic drugs that cause dry mouth, clozapine frequently causes hypersalivation. Clozapine is an antagonist at M3 and M5 receptors and an agonist at M4 receptors. The M4-agonist properties have been associated with clozapine-induced hypersalivation (de Leon et al., 2003a). Other authors have hypothesized that blocking of alpha-receptors may be a contributing factor (Marder & Wirshing, 2004).

Hypersalivation typically occurs at night, and it is often recommended that individuals sleep with a towel on the pillowcase to prevent soaking the pillow. A number of pharmacological agents have been employed to reduce hypersalivation, including anticholinergic drugs such as oral benztropine mesylate (Reinstein, Sirotovskaya, Chasanov, & Jones, 1999); sublingual ipratropium spray (Townsend & Baier, 2004); scopolamine patches (Gaftanyuk & Trestman, 2004); and alpha-blocking agents such as clonidine patches (Grabowski, 1992). The side effect profiles of these agents must be considered (e.g., constipation associated with benztropine- and clonidine-induced hypotension). Chewing gum can be used in combination with benztropine mesylate (Iqbal et al., 2003). Sometimes a simple dose reduction in stabilized individuals may reduce hypersalivation.

2.10. Urinary incontinence

Some individuals (>10%) develop urinary incontinence, particularly at night. Conservative measures are the preferred interventions, including avoiding fluid intake at night, scheduling middle of the night awakenings to empty the bladder and using

enuresis alarms. If necessary, pharmacological agents, such as ephedrine (an alpha-adrenergic agent) and oxubutynine (an anticholinergic agent) may be used (Iqbal et al., 2003).

2.11. Myoclonic jerks

Myoclonic jerks, particularly manifested as orofacial movements (Bak, Bauer, Scaub, Hellweg, & Reischies, 1995), knee buckling or leg folding (Antelo, Stanilla, & Martin-Llonch, 1994) may occur with clozapine therapy. Although there are no good studies, myoclonic jerks appear to be dose related. The movements may represent myoclonic seizures, and some cases have been followed by grand mal seizures (Gouzoulis, Ozdaglar, & Kasper, 1993). Clozapine dose reduction, anticonvulsant use or clozapine discontinuation may be needed for management.

2.12. Extrapramidal effects

Unlike FGA medications, clozapine is relatively free from certain motor side effects, such as parkinsonism, akathisia, and tardive dyskinesia. In fact, there is some evidence that clozapine treatment may improve these conditions (Spivak et al., 1997). The low risk of drug-induced tardive dyskinesia during clozapine therapy has particular promise for individuals with developmental disabilities because of the relatively high risk (20–80%) of antipsychotic-induced dyskinesia in this population (Sajatovic et al., 1994). In addition, reports of benefits in improving some aspects of cognitive and social functioning in individuals without developmental disabilities make clozapine therapy, when properly indicated and monitored, an attractive option for individuals with cognitive impairments.

2.13. Delirium

Clozapine treatment has been implicated in the development of delirium or confusion in the elderly or individuals with cognitive deficits, probably due to its anticholinergic and sedating properties (Young, Bowers, & Mazure, 1998). Consequently, medications with anticholinergic effects and central nervous system (CNS) depressants that increase this risk should be used with caution in individuals taking clozapine.

Dose reduction and slowing the rate of titration may be needed if delirium occurs. Studies suggest that some cases of delirium attributed to clozapine withdrawal are resolved after clozapine is restarted (Iqbal et al., 2003; Stanilla, de Leon, & Simpson, 1997).

2.14. Other side effects

Dizziness occurs in more than 10% of cases, and other side effects (1–10%) include cardiovascular (hypertension, syncope), CNS (tremors, ataxia, slurred speech), gastrointestinal (GI) (heartburn, nausea, vomiting), hematological (eosinophilia, leukocytosis), hepatic (abnormal liver function tests) and visual disturbances. Isolated reports have documented clozapine-related toxic hepatitis, pancreatitis, respiratory arrest, elevation in creatine kinase levels, neuroleptic malignant syndrome, impotence, priapism, allergic

complications and emergence of obsessive compulsive symptoms (Iqbal et al., 2003; Miller, 2000; NPC, 2003).

3. Dosage

In the U.S., clozapine dosage for adults is up to 900 mg/day although, in rare cases, patients have required higher doses to reach therapeutic levels (Bender & Eap, 1998).

4. Blood levels

Several controlled clozapine-level studies have been conducted in individuals with schizophrenia who are treatment refractory. Most studies recommend plasma clozapine therapeutic concentrations higher than 350 ng/ml (Hasegawa, Gutierrez-Esteinou, Way, & Meltzer, 1993; Kronig et al., 1995; Perry, Miller, Arndt, & Cadoret, 1991; VenderZwaag et al., 1996), with a highest of 420 ng/ml (Potkin et al., 1994). There is no published information on monitoring clozapine levels in individuals with developmental disabilities. However, using blood levels and taking into account drug–drug interactions, appear to be good practices. Five basic principles need to be considered to interpret clozapine blood levels.

4.1. Standardization

All of the clozapine-level studies used trough steady-state levels. Trough means that levels are drawn in the early morning before the morning dose is administered and approximately 12 h after the last dose. A steady-state level is usually estimated to require 5–6 half-lives. The elimination half-life of clozapine, which is reported to be shorter than that of FGA, is estimated to be 12 h with a range of 6–33 h. The rounded average of the half-life is 24 h (de Leon, Henighan, Stanilla, & Simpson, 1996). Thus, a good rule of thumb for obtaining clozapine levels is to wait at least 1 week after the last clozapine dose change and after any important changes in major factors that influence the levels (e.g., smoking, caffeine intake, and the concomitant use of inhibitor or inducer drugs). One needs to be sure of compliance with treatment during the week prior to obtaining levels. When an abnormally low level is observed, one should first suspect medication non-adherence and, second, rapid metabolism.

4.2. Parent versus metabolite levels

Most clozapine-level studies also measure concentrations of norclozapine, the primary metabolite of clozapine. Some in vitro studies suggest that norclozapine may bind to brain receptors, but there is no clinical evidence that norclozapine contributes to therapeutic activity, and limited information suggests that it may contribute to clozapine's side effects (de Leon et al., 2003a). Thus, although norclozapine levels may assist in monitoring clozapine metabolism, they do not seem to predict therapeutic response (de Leon & Diaz, 2003).

4.3. Therapeutic window

The width of the therapeutic window determines the clinical significance of changes in plasma levels. Compared to other NGA, clozapine has a narrow therapeutic index (de Leon, 2004a). The lower limit of the window (350 or 450 ng/ml) is the lowest level that is associated with therapeutic efficacy, and the upper limit (1000 ng/ml) is the level above which toxicity occurs, including the risk of seizure and severe sedation (Simpson & Cooper, 1978).

4.4. Normal variations

Clinicians frequently fail to understand that a single clozapine level must be viewed with caution and that a pattern change in several levels is easier to interpret. Laboratory, technical and natural variations can cause some day-to-day variations in clozapine levels, even after assuming stability of all possible confounding factors such as timing of collection, dose and schedule, and drug interactions. There is limited information on normal variations of clozapine levels seen in the naturalistic setting (de Leon & Diaz, 2003; Kurz et al., 1998). Based on this information, it seems reasonable to suggest that only a change by a factor of two is probably meaningful from the clinicians' perspective (de Leon, 2004b). This means that if an individual has a clozapine level of 500 ng/ml, the next one in the same stable conditions should not be >1000 or <250 ng/ml. However, a change from 500 to 400 ng/ml is probably not significant.

4.5. Relationship between dose and therapeutic level

In typical doses, clozapine appears to have a linear relationship between doses and concentrations (first order kinetics), particularly within the same individual (Choc et al., 1987). Pharmacologists use a simple formula, the concentration–dose ratio (C/D), to represent this relationship (de Leon, 2004b). Plasma clozapine concentrations exceeding 350 ng/ml are described as therapeutic, with most individuals requiring a dose of 300–600 mg/day to reach these levels. Assuming that each individual needs a dose of 300 mg/day to reach a level of 350 ng/ml, this provides a C/D of 1.2 (350/300). Conversely, assuming that each individual needs a dose of 600 mg/day, this provides a C/D of 0.6 (350/600). Therefore, the average individual taking clozapine has a C/D of 0.6–1.2. Individuals requiring higher clozapine doses to reach therapeutic concentrations have a lower C/D. For example, one individual thought to have a high capacity to metabolize clozapine had a C/D < 0.17 (Bender & Eap, 1998). In summary, it appears that the average individual may need at least 300 mg/day to reach a therapeutic level (Simpson et al., 1999).

5. Metabolism

The clozapine dosing recommendations provided by package labels are generated by the dose response of the “average subject” in double-blind studies where most co-prescriptions are forbidden. Therefore, these recommendations may not be appropriate for

many individuals who cannot be considered “average”. Examples include individuals who lack or have too much of the enzyme responsible for clozapine metabolism, and/or individuals who take other medications that significantly influence the metabolism. Approximately 70% of clozapine metabolism is explained by the cytochrome P450 1A2 (CYP1A2) (Bertilsson et al., 1994). Thus, factors influencing CYP1A2 may affect C/D ratio. These factors are either genetic or environmental (e.g., interactions with factors that act as enzyme inhibitors or inducers).

5.1. Genetic factors

Until very recently, there were no reports of individuals lacking CYP1A2 (poor metabolizers), but there were reports of a few individuals having too much CYP1A2 (rapid metabolizers) (Bender & Eap, 1998). Current knowledge suggests that it is very unlikely (<1%) that polymorphic genetic variations may explain unusual clozapine levels.

5.2. Drug interactions

Drug interactions may be important determinants of clozapine doses and levels. The following is an outline of significant interactions that physicians prescribing clozapine need to consider.

5.2.1. Anticonvulsants

Three “old” anticonvulsants, phenobarbital, primidone and phenytoin, are powerful inducers of clozapine metabolism (de Leon, 2004b). Although there is limited available information, one should expect that an individual with developmental disabilities taking phenytoin may need doses four times higher than he/she would need if not taking phenytoin (Miller, 1991). The inductive effects of these drugs may typically take 2–3 weeks to disappear after discontinuation. Therefore, if an individual is taking phenytoin and clozapine, physicians discontinuing phenytoin should expect a slow increase in clozapine levels over a period of 2–3 weeks by a factor of four (de Leon, 2004b). Because of their interactions with clozapine, it appears safer to avoid the co-administration of these drugs or to carefully monitor their use with blood level determinations and to obtain consultation. At present, there are no data to suggest that gabapentin, levetiracetam, topiramate and tiagabine interact with clozapine. It is not yet clear if lamotrigine interacts with clozapine. Available information indicates that valproic acid is probably the anticonvulsant of choice in individuals taking clozapine because it is free of major interactions. Some minor effects of valproic acid on clozapine levels have been described, but they do not appear to be clinically significant (de Leon, 2004b).

5.2.2. Antidepressants

Tricyclic antidepressants should not be co-prescribed with clozapine because they may increase clozapine levels and, more importantly, exacerbate the risk of cardiovascular toxicity due to their prolongation of the QTc interval.

Most serotonin selective reuptake inhibitors (SSRIs) appear to be metabolic inhibitors. Fluvoxamine, in particular, appears to be a very strong inhibitor of CYP1A2 (Hiemke et al.,

1994). It has been used to lower clozapine dose for economic reasons, but it appears safer to avoid it. Similarly, sertraline (Pinninti & de Leon, 1997) and fluoxetine (Centorrino et al., 1994) may increase clozapine levels and should be avoided. It must be remembered that the metabolic inhibitory effect of fluoxetine may last for months after its discontinuation. Safer alternatives that are relatively free of major interactions include paroxetine, citalopram, escitalopram, venlafaxine and mirtazapine.

5.2.3. *Mood stabilizers*

Lithium does not change clozapine levels, and has been used to increase absolute neutrophil count in individuals taking clozapine. Carbamazepine and oxcarbazepine should be avoided due to the risk of agranulocytosis. As described above, valproic acid is unlikely to cause major interactions. More studies are needed to provide recommendations regarding the use of lamotrigine.

5.2.4. *Antipsychotics*

Clinicians sometimes prescribe antipsychotics to augment clozapine response. Although there are no experimental data to support this practice, physicians should consider the effects of added blocking of brain receptors because many antipsychotics block the same dopaminergic, adrenergic, serotonergic, muscarinic and histaminic receptors involved in clozapine. In addition, some antipsychotics may increase clozapine levels.

Among the FGA, perphenazine and other phenothiazines clearly have the potential to increase clozapine levels (Cooke & de Leon, 1999). Haloperidol is probably relatively free of pharmacokinetic interactions with clozapine although it has not been systematically studied.

There are almost no published studies on adding NGA to clozapine. The metabolism of both clozapine and olanzapine is mainly dependent on the same enzymes (CYP1A2 and UDP-glucuronosyltransferases) (de Leon, 2003b). Thus, we can assume that clozapine can increase olanzapine levels and olanzapine can increase clozapine levels (clozapine has a narrower therapeutic window). If olanzapine is co-prescribed, careful monitoring of clozapine levels is warranted. There is some controversy as to whether risperidone can increase clozapine levels, but current knowledge suggests that it probably does not. It is reasonable to expect that quetiapine and aripiprazole are unlikely to increase clozapine levels although there are no clinical data to support this assumption. Ziprasidone should not increase clozapine levels, but it is better to avoid it due to the risk of QTc prolongation.

5.2.5. *Benzodiazepines*

The interaction between benzodiazepines and clozapine has been described in a few individuals during the first days of clozapine therapy, usually within 24–48 h after the first clozapine dose (Cobb, Anderson, & Seidel, 1991). Side effects of this interaction may include lethargy, ataxia, loss of consciousness and, rarely, respiratory arrest. Respiratory arrest has been reported in seven cases in a sample of 12,000 individuals treated with clozapine, but only two of these cases were associated with the combination of benzodiazepines and the first clozapine dose (Finkel & Schwimmer, 1991). Of 162 individuals treated with a combination of clozapine and benzodiazepines, respiratory arrest

occurred in one individual who suffered from liver impairment (Klimke & Klieser, 1994). The occurrence of respiratory arrest during the co-administration of clozapine and benzodiazepines appears to be an idiosyncratic reaction. However, it is safer to avoid benzodiazepines the week before starting clozapine and during the first week of dose titration.

5.2.6. *Other medications*

The fluoroquinolones, particularly ciprofloxacin and norfloxacin, are powerful CYP1A2 inhibitors and are expected to increase clozapine levels (Raaska & Neuvonen, 2000). Other fluoroquinolones, including gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin and trovafloxacin, do not appear to inhibit CYP1A2 and can be safely prescribed for individuals taking clozapine. Although macrolides, such as erythromycin and clarithromycin, are very powerful inhibitors of a hepatic enzyme that does not metabolize clozapine, close monitoring is recommended when adding to clozapine (Hagg et al., 1999). Cimetidine should be avoided in individuals taking clozapine (Szymanski, Lieberman, Picou, Masiar, & Cooper, 1991).

5.3. *Dietary interactions*

Some foods induce CYP1A2, particularly charbroiled food and cruciferous vegetables (e.g., broccoli, brussel sprouts and other plants belonging to the Cruciferae or Brassicaceae family) may reduce clozapine levels slightly, but the decrease in levels is unlikely to be clinically significant (Vistisen, Loft, & Poulsen, 1991). Grapefruit juice does not appear to inhibit clozapine metabolism, but it should not be administered to individuals with developmental disabilities due to the risk of interactions with multiple drugs.

The metabolism of caffeine is highly dependent (>90%) on CYP1A2 and caffeine intake elevates the risk of increased clozapine levels (de Leon et al., 2003b). However, only high caffeine intake may have clinically significant interactions with clozapine. In the U.S., a 5 oz cup of brewed coffee is estimated to contain 85 mg of caffeine; instant coffee, 65 mg per cup; decaffeinated coffee, 3 mg, and tea, 40 mg. Caffeinated sodas including colas, contain 40 mg of caffeine in a 12 oz can (or one sixth of a 2 l bottle) (de Leon et al., 2003b). Caffeinated over-the-counter medicines may have up to 200 mg of caffeine in a single pill.

There are no data regarding the level of caffeine intake that is safe for individuals taking clozapine. Steady caffeine doses in an individual stabilized on clozapine should not concern clinicians. However, it may be important to warn the individual to avoid dramatic changes (up or down) in caffeine intake. Although no published study defines what a dramatic change is, caution has been recommended with increases or decreases of daily caffeine intake of >1 cup of coffee (or two cans of caffeinated sodas) in non-smokers and >3 cups (or six cans of caffeinated soda) in smokers. For example, when a smoker taking clozapine increases caffeine intake by three cups of coffee (e.g., from 2 to 5 cups per day), clinicians should watch for increased side effects due to increased clozapine levels. When a non-smoker taking clozapine decreases caffeine intake by two cans (e.g., from 4 to 2 cans per day), clinicians should be alert to possible loss of clozapine response due to decreased levels (de Leon, 2004a).

5.4. Smoking

Tobacco smoking by-products, particularly the polycyclic aromatic hydrocarbons, are metabolic inducers, and also induce clozapine metabolism. Given that inducers require new enzyme synthesis for their effects, they usually take several weeks to reach maximum effects. The effects may take a few weeks to disappear as well. Case reports of clozapine toxicity, including seizures, after smoking cessation suggest smoking induced effects take at least 2–4 weeks to disappear (McCarthy, 1994; Skogh, Bengtsson, & Nordin, 1994; Zullino, Delessert, Eap, Preisig, & Baumann, 2002).

Smoking cessation would probably cause clozapine levels to increase by a factor of 1.5, 2–4 weeks later. Similarly, if a non-smoking individual starts to smoke heavily (>1 pack/day), the clinician may need to consider increasing the clozapine dose by a factor of 1.5 over 2–4 weeks. Checking for side effects and measuring clozapine level may be prudent because the 1.5 factor is a gross approximation (de Leon, 2004a).

It appears that gender may play a role as well. The available information is limited, but suggests that an average female non-smoker may require clozapine doses around 300 mg/day to reach therapeutic levels, while an average male heavy smoker may require high doses (around 600 mg/day). The doses for male non-smokers and female smokers fall somewhere in between 300 and 600 mg/day (Perry, Bever, Arndt, & Combs, 1998; Rostami-Hodjegan et al., 2004). These average results may not apply to specific individuals especially if other factors that may affect clozapine metabolism are not stabilized. In summary, stable smoking may not be an important factor, but radical changes such as cessation or starting heavy smoking may influence clozapine levels.

5.5. Respiratory infections

Respiratory infections can inhibit CYP1A2 because cytokines released during the infection decrease the enzyme activity and synthesis (Abdel-Razzak et al., 1993). Clinicians caring for individuals with developmental disabilities who are taking clozapine must monitor for signs of toxicity, including severe sedation, myoclonus or even seizures, if the individual develops serious respiratory infections, particularly with fever. If any of these signs and symptoms appear, the dose of clozapine should be decreased at least by half until the individual has recovered from the infection (de Leon, 2004c).

6. Guidelines

We provide the following guidelines for prescribing psychiatrists. The procedures in these guidelines may not fully account for all of the possible risks of treatment in individuals with developmental disabilities because of the current paucity of well-controlled studies in this population. Thus, the guidelines will need to be updated as new knowledge becomes available. Nevertheless, we believe that these guidelines are a useful resource for psychiatrists and other physicians who treat mental illness and challenging behaviors in individuals with developmental disabilities. Prescribing psychiatrists must

make a clinical judgment on the use of clozapine with individuals with developmental disabilities on a case-by-case basis using the best available evidence.

6.1. *Decision about initiating treatment*

Obtain a careful history and consider individuals for a clozapine trial if all of the following four criteria are met.

6.1.1. *Cooperation*

Determine that the individual is willing to cooperate with treatment and periodic venipuncture. In addition, ascertain that the individual (and/or guardian) is willing to sign the consent form.

6.1.2. *Absence of major contraindications*

Determine that the individual does not have any of the following major contraindications to clozapine use: myeloproliferative disorder, history of clozapine-induced agranulocytosis or severe leukopenia (see blood monitoring), current WBC count less than 3500 cmm^{-1} or absolute neutrophil count (ANC) less than 1500 cmm^{-1} , concurrent use of other drugs known to suppress bone marrow function (e.g. carbamazepine, captopril, propylthiouracil, penicillamine, sulfonamides and antineoplastic agents), hypersensitivity to clozapine, loxapine or amoxapine, severe CNS depression, uncontrolled epilepsy, severe renal or cardiac disease, active liver disease and progressive liver disease.

6.1.3. *Careful consideration of any relative contraindication*

Be cautious in prescribing clozapine if the individual has any of the following relative contraindications to clozapine therapy: history of a seizure disorder that required anticonvulsant medication to achieve control, cardiovascular disease, prostatic hypertrophy, narrow angle glaucoma, use of other drugs known to lower seizure threshold, use of CNS depressants (e.g., benzodiazepines and alcohol) and pregnancy. In these situations, discuss the case with the individual's primary care physician and/or specialist, and document this in the chart.

If the individual is taking other drugs known to potentially suppress bone marrow function, start clozapine only after these drugs have been discontinued. In these situations, discuss the case with the individual's primary care physician and/or specialist, and document this in the chart. Stop benzodiazepines 1 week before starting clozapine and, if needed, restart 1 week after clozapine has been started. If there is a history of a seizure disorder or current seizure disorder is under reasonably good control, obtain electroencephalogram (EEG) and neurological consultation before considering clozapine and document this in the chart.

6.1.4. *Indications*

Clozapine trial is indicated if at least one of the following clinical situations is present:

- a. The individual has a current DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder and, by history, has failed to tolerate or respond adequately to treatment with at

least one FGA and all other NGAs. A trial with all NGAs is more conservative than schizophrenia guidelines (Miller et al., 2004), but it appears reasonable to have a more conservative approach in individuals with developmental disabilities than in those without them. Document in the chart that clozapine is being used for treating refractory psychosis and that the individual has failed to tolerate or respond adequately to other antipsychotic medication. If possible, describe the duration and dose of each antipsychotic trial. In cases when it is known that another antipsychotic agent has been tried, but precise history is absent, consult with the individual and/or guardian about the merits of repeating another trial of the same antipsychotic.

- b. The individual has severe persistent aggressive or self-injurious behavior with evidence that a behavioral treatment was implemented as part of a formal training program and found to be ineffective. Document the specific indication.
- c. The individual suffers from antipsychotic-induced progressive tardive dyskinesia, particularly if truncal-axial involvement is present and an antipsychotic treatment is needed. Document the specific indication.
- d. The individual has DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder and is considered to be at high risk for suicide. Document the specific indication.
- e. The individual suffers from complicated polydipsia, particularly with symptomatic hyponatremia. Document the specific indication.

6.2. Clozapine initiation

6.2.1. Informed consent

Obtain informed consent prior to treatment initiation and document in the chart. Inform the individual and/or guardian of at least the following:

- a. The risk of agranulocytosis and need for weekly blood tests during the first 6 months and every other week thereafter.
- b. The results of blood tests will be shared with the pharmacist and CNR, and the drug will not be supplied if the blood is not obtained.
- c. Side effects (see Section 2, above).
- d. The risks involved in suddenly stopping clozapine.
- e. The need to contact the prescribing physician if clozapine is not taken for 48 h or longer.
- f. Caution regarding pregnancy and if the individual is breast feeding.
- g. Instructions to tell any health care professional with whom he/she come in contact that he/she is on clozapine.

6.2.2. Baseline assessment

Obtain complete blood count (CBC), EKG, EEG and neurological consultation (if the individual has a current or history of seizure disorder), fasting blood glucose level, triglycerides and cholesterol levels and Dyskinesia Identification System: Condensed User Scale (DISCUS) rating (Sprague & Kalachnik, 1991).

6.2.3. Clozapine trial

A typical trial of clozapine may include the following steps:

- a. Contact CNR (#800-448-5938) for individual and physician registration and to verify that the individual did not develop clozapine-related agranulocytosis or leukopenia in the past. Initiate treatment only after an authorization number has been assigned by CNR.
- b. Ideally, discontinue other antipsychotic medication or titrate down when clozapine is being titrated up. Individuals with developmental disabilities requiring clozapine treatment are probably very difficult to treat, and it may not be prudent to discontinue the other antipsychotic before determining if clozapine is going to be tolerated or will be effective. It is reasonable to avoid adding clozapine to more than one antipsychotic and, if a phenothiazine or olanzapine is the baseline medication, consider starting with 12.5 mg as first dose with slower titration. If the baseline medication is a long-acting depot preparation, change to oral preparation at the next scheduled dose.
- c. Due to its sedating properties, clozapine may be better administered with a larger dose at night and a smaller dose in the morning (e.g., 66% of dose at night and 33% at early morning). To avoid orthostatic changes, start with first dose at night and follow vital signs closely, particularly in the first week or when dose is changed.
- d. To minimize the occurrence and risk of serious adverse effects associated with clozapine therapy, initiate therapy cautiously with a slow dose titration. For example, begin titration with a dose of 25 mg at night and reach 100 mg/day at the end of the first week, using 25 mg increments. During the second week, if the individual tolerates the titration well, implement two increments of 50 mg (or four increments of 25 mg) to reach 200 mg/day at the end of the second week. In the third week, if the individual tolerates the titration well, implement two increments of 50 mg to reach 300 mg/day at the end of the third week (NPC, 1997; Simpson et al., 1999).
- e. Begin with a dose of 12.5 mg in the presence of old age, clozapine metabolic inhibitors, or high side effects risk.
- f. A dose of 300 mg/day may be therapeutic in some individuals but not in others. Thus, draw a blood level 1 week after reaching this dose to determine further need for an increase in dose. If the individual is taking another antipsychotic, this may be the time to consider titrating down and discontinuing in a few days. If the antipsychotic has been discontinued, delay assessing blood levels for 1 week after discontinuation or draw blood levels twice.

Use the linear relation of C/D to estimate target clozapine dose. If in doubt, draw another blood level when the target dose is reached. The expenses incurred in monitoring clozapine levels are small when compared to the safety they provide. Further, monitoring may indicate that the dose can be lowered, thereby producing savings in the longer-term.

After reaching 300 mg/day with sub-therapeutic blood levels and no clinical response, increase the dose by 50 mg/day according to tolerance and observe for 2–3 days before increasing the dose. When prescribing doses higher than 300 mg/day,

remember that rounded doses (400, 500, 600, etc.) are easier to administer for months and years. It is simpler to administer one 100 mg tablet than two or three 25 mg tablets. For example, a dose of 400 mg/day (e.g., 100 mg tablet in the morning and three 100 mg tablets at night) is easier to administer than a dose of 375 mg/day (e.g., one 100 mg in morning, and two 100 mg plus three 25 mg at night).

In individuals without developmental disabilities, using blood levels after reaching 300 mg/day is more conservative than the generally accepted practice of obtaining a level for doses higher than 600 mg.

6.3. Guidelines for clozapine trials in individuals with developmental disabilities who are non-responders

6.3.1. Individuals with developmental disabilities who have treatment-resistant schizophrenia

- a. There is no consensus as to the total time required to achieve an optimal response to clozapine therapy. It has been reported that individuals who respond to clozapine typically show their response within 8 weeks of a change in dosage (Conley, 1998). Based on current available information, continue treatment for at least 3 months with a dose associated with clozapine levels of at least 350 ng/ml for individuals with treatment-resistant schizophrenia before determining their response to treatment.
- b. For individuals who do not respond or respond only partially to clozapine, published practice guidelines support continuing clozapine and augmenting treatment with another NGA (e.g., risperidone, quetiapine, olanzapine, ziprasidone, or aripiprazole) or an FGA medication (Miller et al., 2004). Use agents with a previous history of partial response. As mentioned earlier, be careful with phenothiazines and olanzapine. Discuss with the individual/guardian before making a decision, and document this discussion in the chart.
- c. There are no controlled data to provide guidance for the use of any single antipsychotic or any combination of antipsychotics for individuals who do not respond adequately to clozapine and to clozapine augmentation. However, published practice guidelines suggest discontinuation of clozapine and attempting one final trial of antipsychotic monotherapy, preferably with an agent with a history of partial response, before resorting to antipsychotic polypharmacy (Miller et al., 2004).
- d. If all of the above fails, attempt a combination treatment with two NGA agents, or an NGA and an FGA, or two FGA agents or an antipsychotic and a mood stabilizer.

6.3.2. Individuals with developmental disabilities who engage in self-injurious behavior

- a. There is not enough information to provide recommendations regarding the duration and dose for clozapine trials in these individuals. However, it may be reasonable to undertake at least a 3-month trial of a dose associated with clozapine levels of at least 350 ng/ml.
- b. If individuals fail to respond satisfactorily, published practice guidelines (Rush & Frances, 2000) suggest to:

- (i) Discontinue clozapine and switch to a different atypical antipsychotic medication or a mood stabilizer or an SSRI (if no response), or
- (ii) continue clozapine and add a mood stabilizer or an SSRI (if partial response).

6.3.3. *Individuals with developmental disabilities who exhibit aggressive/destructive behavior in the absence of psychotic symptoms*

There is not enough information to establish the duration and dose of clozapine trials in these individuals. However, it may be reasonable to undertake at least a 3-month trial of a clozapine dose associated with levels of at least 350 ng/ml. If symptoms continue, published practice guidelines (Rush & Frances, 2000) recommend to:

- a. Discontinue clozapine and switch to a mood stabilizer or a different atypical antipsychotic (if no response), or
- b. continue clozapine and add a mood stabilizer (if partial response).

6.3.4. *Individuals with developmental disabilities and abnormal movements*

- a. There is not enough information to establish the duration and dose of clozapine trial in these individuals. However, it may be reasonable to use the lowest dose possible and wait at least 3 months for a clinical response.
- b. If there is no obvious improvement in abnormal movements, consider discontinuing clozapine and/or consulting a neurologist with expertise in movement disorders.

6.3.5. *Individuals with developmental disabilities and polydipsia*

- a. Careful follow up using biological measures in individuals with schizophrenia and polydipsia suggests that the positive effects of clozapine on hyponatremia occur early, usually within 2 weeks, and with doses as low as 100 or 200 mg/day (de Leon, Verghese, Stanilla, Lawrence, & Simpson, 1995). However, polydipsia may take up to 12 weeks to improve (Verghese et al., 1998).
- b. Based on available information, it is reasonable to use clozapine doses up to 300 mg/day for individuals with complicated polydipsia, together with a water restriction behavioral program using the target weight method (Goldman & Luchins, 1991).

6.3.6. *Individuals with developmental disabilities and other psychiatric conditions*

Augment clozapine in a targeted manner if the individual has a specific symptom that is not responsive to clozapine therapy. For example, add SSRI for depression, a mood stabilizer for mood instability, or buspirone for an agitated anxiety state.

6.4. *Monitoring for side effects*

6.4.1. *Oral temperature*

Monitor for oral temperature twice a day (before giving clozapine doses) using the Clozapine Side Effects Rating Scale (CSERS) (Appendix A). Repeat the measure after 15 min if there is an oral temperature above 99.8 F. Administer clozapine if the temperature is within a normal range; otherwise, consult a physician before administering the next dose.

If oral temperature is elevated, consider the possibility of infection or benign hyperthermia (i.e., low grade fever with no cause). Pay special attention to the possibility of respiratory infection. The presence of fever is a red flag due to the possibility of agranulocytosis, but remember that agranulocytosis is rare (<1%), particularly after 6 months of treatment. Moreover, it can be easily ruled out by drawing blood counts.

6.4.2. *Pulse and blood pressure*

Monitor for pulse and blood pressure twice a day (before giving clozapine doses) using the CSERS, and ask for signs of orthostatic changes if the individual can answer. Record pulse and blood pressure after the individual has been sitting for 3 min and then after the individual has been standing for 2 min. Orthostatic changes cannot be measured in individuals who cannot stand up; thus, it is important to monitor these individuals closely until the dose is stable.

If blood pressure or pulse lies outside the parameters (given below), repeat the measure after 15 min. Give clozapine when blood pressure or pulse falls within accepted parameters, or request a physician assess the individual should the measure continue to fall outside accepted parameters. The parameters are (Simpson et al., 1999):

- a. Systolic blood pressure below 90 mm or above 150 mm.
- b. Diastolic blood pressure below 60 mm or above 100 mm.
- c. Drop greater than 20 mm in systolic or diastolic pressure between sitting and standing.
- d. Pulse greater than 120 min^{-1} or less than 60 min^{-1} .

Careful monitoring and delayed titration allow individuals to develop tolerance to orthostatic changes and tachycardia. Thus, in most cases, changes disappear with time. Assess individuals with tachycardia for the risk of myocarditis.

6.4.3. *Complete blood count*

Monitor CBC and differential count as follows (NPC, 2004):

- a. Obtain weekly CBC for the first 6 months of treatment, then every other week for individuals with WBC of $\geq 3500 \text{ mm}^{-3}$ and ANC of $\geq 1500 \text{ mm}^{-3}$.
- b. Review and initial reports of blood counts prior to filing in the individual's record. Send a duplicate copy of the report to pharmacy, record WBC prior to dispensing, and dispense a maximum supply of 7 days during the first 6 months and 14 days thereafter.
- c. If CBC reveals WBC less than 3500 mm^{-3} , or if there is a substantial drop from baseline, or if immature forms are present, repeat WBC and do a differential count. A substantial drop is defined as a single or cumulative drop of 3000 mm^{-3} or more within 3 weeks.
- d. If repeat CBC reveals mild leukopenia (i.e., WBC between 3000 and 3500 mm^{-3}), continue clozapine therapy and obtain twice weekly WBC and differentials until the WBC is above 3500 mm^{-3} . Closely monitor individuals for infections and treat any infections promptly and appropriately.
- e. If WBC is below 3000 mm^{-3} or ANC is less than 1500 mm^{-3} (moderate leukopenia), discontinue clozapine at once, notify CNR, institute daily WBC and differential counts, monitor individual for flu-like symptoms and for other signs and symptoms of infection.

The pharmacy shall not dispense clozapine when WBC falls to less than 3000 mm⁻³ or ANC falls to less than 1500 mm⁻³.

- f. If WBC returns to levels greater than 3000 mm⁻³ and ANC returns to levels greater than 1500 mm⁻³ and no signs or symptoms of infection are present, resume clozapine therapy and continue twice-weekly WBC with differentials until WBC returns to levels greater than 3500 mm⁻³.
- g. If any signs or symptoms of infection develop and/or WBC or ANC fails to return to levels greater than 3000 or 1500 mm⁻³, respectively, obtain an internal medicine consultation.
- h. If WBC is less than 2000 mm⁻³ or ANC is less than 1000 mm⁻³ (severe leukopenia or agranulocytosis), discontinue clozapine immediately with no rechallenge, notify CNR, obtain daily WBC with differentials and obtain a consultation with a hematologist immediately. Individuals with WBC of less than 1000 mm⁻³ require immediate hospitalization and isolation.
- i. Besides following CNR guidelines closely, remember that clozapine can destroy granulocytes but spare other white counts. Therefore, ANC is a better measure than the WBC to monitor the risk of agranulocytosis. The ANC varies greatly from individual to individual; a few individuals with very high ANC may have more room to drop to the ANC levels described by CNR. Thus, be alert to drops in ANC that are unusual for a given individual but may not reach the CNR thresholds. An example would be if most of an individual's ANCs during several months ranged from 5000 to 7000 mm⁻³, with a few ANCs in the range of 3200–4600 mm⁻³. If the ANC drops to 2000 mm⁻³, it is still above the guideline, but this ANC at this level is clearly unusual for this individual. Also, remember that viral infections sometimes cause neutropenia.

6.4.4. *Weight, serum glucose and lipids*

Monitor weight and serum glucose and lipids (Henderson et al., 2000; Lebovitz, 2001; Wirshing et al., 2002) as follows:

- a. Check weight at least monthly. Weight gain should initiate dietary interventions and nutritional consultation.
- b. Repeat baseline measurements of fasting blood glucose, triglycerides and cholesterol every 3 months.
- c. Obtain glucose tolerance test (2 h plasma glucose level post 75 g oral glucose load) and medical consultation if fasting glucose level is 110 mg/dl or higher.
- d. Obtain medical consultation and provide interventions as appropriate for abnormal or rising triglyceride or cholesterol levels.
- e. Be alert to the possibility of diabetic ketoacidosis.

6.5. *Discontinuation of clozapine*

6.5.1. *Sudden discontinuation*

Sudden discontinuation of clozapine has been associated with withdrawal symptoms. Some individuals have symptoms suggestive of a cholinergic rebound including nausea,

vomiting, diarrhea, headache, agitation, confusion and diaphoresis. These symptoms are probably explained by the antimuscarinic properties of clozapine and appear to respond to anticholinergic treatment (de Leon, Stanilla, White, & Simpson, 1994). Other individuals appear to have worsening psychosis and/or abnormal movements (Stanilla et al., 1997).

If clozapine has to be discontinued suddenly due to side effects, consider adding another NGA to cover withdrawal psychosis or withdrawal movements. If there are signs of cholinergic rebound, add anticholinergics (e.g., 2–6 mg of benztropine mesylate or 5–15 mg/day of trihexphenidyl) and monitor closely because higher doses may be needed (de Leon, Stanilla, White, & Simpson, 1994).

6.5.2. *Lack of therapeutic response*

If clozapine is to be discontinued due to lack of therapeutic response, taper off slowly over a period of a few weeks. At least 2–3 weeks is needed for planned discontinuation of a dose of 600 mg/day. Clozapine is too toxic, inconvenient and expensive to be continued after 6 months of a presumed therapeutic dose if there is no clear response.

6.5.3. *Interruption of clozapine therapy*

If clozapine therapy is interrupted for a period of 48 h or more, restart clozapine therapy with a 25 mg tablet and titrate upward as if the individual is new to clozapine. If the individual is doing very poorly and a faster schedule appears necessary, seek a consultation with a psychiatrist who has extensive experience with clozapine therapy.

6.5.4. *Following discontinuation of clozapine therapy*

After discontinuation of clozapine therapy, request four or more weekly blood tests for CBC with differential.

7. Summary

Several studies and meta-analytic reviews have demonstrated the efficacy of clozapine in treating psychotic symptoms refractory to other antipsychotic medications. Furthermore, clozapine can be an effective treatment for conditions that do not involve the presence of current psychotic symptoms. This unique efficacy makes it an attractive option for individuals with developmental disabilities. Although research on clozapine in this population is rather limited, individuals who have failed behavioral and other drug treatments and exhibit challenging behaviors that require pharmacological interventions appear to be good candidates for treatment with this drug. In the absence of consensus guides, we presented a set of guidelines to ensure proper utilization of clozapine in individuals with developmental disabilities. The procedures contained in these guidelines may not fully account for all of the possible risks of treatment in this population because of the limited studies available; thus, there will be a need to periodically update this guide as new knowledge becomes available. Nevertheless, we believe that these guidelines will provide a useful resource for psychiatrists who treat challenging behaviors in individuals with developmental disabilities.

8. Conflict of interest

Jose de Leon, M.D., lectured once in 1997 supported by Novartis and, between 1992 and 1995, participated in a clozapine double-blind study that was supported by the U.S. National Institute of Mental Health grant MH-47162 to George M. Simpson, M.D. and Richard C. Josiassen, Ph.D. Novartis Research Institute provided free medication for the clozapine double-blind study. More recently, in the past 2 years, Dr. de Leon has been on the advisory board of Bristol-Myers Squibb and AstraZeneca. He has received researcher initiated grants from Eli Lilly and Roche Molecular Systems, Inc., and lectured once with the support of Eli Lilly. Drs. Sabaawi and Singh do not have any conflict of interest with pharmaceutical drug companies.

Acknowledgments

We thank Dr. Judy Singh and Ms. Rachel Myers for assistance in the preparation of the guidelines.

Appendix A. Clozapine side effects rating scale¹

Date: _____ Time: _____

Rater: _____

Building: _____

A. Record pulse and blood pressure:

Seated position after three minutes: BP _____ P _____

Standing two minutes: BP _____ P _____

B. Record oral temperature: _____

C. Nurse's objective observations (check present/absent):

	Absent	Present
1. Temperature above 99.8 orally	_____	_____
2. Systolic BP below 90mm or above 150mm	_____	_____
3. Diastolic BP below 60mm or above 100mm	_____	_____
4. Greater than 20mm drop of systolic or diastolic between sitting and standing	_____	_____
5. Pulse over 120/min or less than 60/min	_____	_____

Note: If any item lies outside parameters, repeat measure after 15 minutes. If then within parameters, give clozapine as ordered. If still outside parameters, call psychiatrist to assess.

D. Observe and if possible ask patient if s/he has any physical problems or complaints (check present/absent):

	Absent	Present
1. Symptoms/signs of infection (e.g. sore throat or cough, ulcers mouth; chills; rectal soreness/itching; vaginal soreness/itching; urinary frequency/burning)	_____	_____
2. Salivation	_____	_____
3. Drowsiness/sedation	_____	_____
4. Falling	_____	_____
5. Leg folding or knee buckling	_____	_____
6. Dizziness	_____	_____
7. Constipation	_____	_____
8. Urinary incontinence	_____	_____
9. Other (specify):	_____	_____



¹ A modification of the scale originally developed for the study by Simpson et al. (1999).

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