DSH PSYCHOTROPIC MEDICATION Operational Procedures

APPENDIX -- CLOZAPINE HISTORICAL REVIEW:

Directive statements and procedures in this chapter are informational and advisory in nature. Prescribing should be based on Chapter 15, Clozapine Protocol.

General Information:

Background:

Clozapine is an atypical or second-generation antipsychotic (SGA) medication manufactured by Novartis and others and marketed under the trade names in the U.S. of Clozaril and FazaClo (orally dissolving tablet).

Clozapine is indicated for use in individuals with schizophrenia spectrum disorders who are either resistant or intolerant to other antipsychotic drugs, with therapeutic benefits in up to 60% of cases (Kane, Honigfiled and Singer, et al. 1989; Baldessarini and Frankenburge, 1991).

The efficacy of clozapine has been proven to be superior to that of the conventional or first-generation antipsychotic (FGA) agents (Singer and Law, 1974; Kane, et al, 1988) and the other SGA agents (Conely and Buchanan, 1997).

Both positive and negative symptoms appear to improve with clozapine treatment (Tandon and Goldman, 1993).

Clozapine can help achieve a treatment response characterized not only by symptom reduction but also by improvement in certain aspects of cognitive functioning, social functioning and quality of life; decreased need for hospitalization; and enhanced adherence to treatment (Meltzer, Burnett and Bastani, et al., 1990; Meltzer, 1992; Grace, Bellus and Raulin, et al., 1996).

Significant reduction in suicidal behavior among schizophrenic individuals has been attributed to clozapine treatment (Meltzer, Alphs and Green et al., 2003; Barclay, 2003).

In addition to its proven efficacy among individuals with schizophrenia, clozapine treatment has been shown to be effective in individuals with:

- Schizoaffective and psychotic mood disorders (McElroy, 1991; Zarate, Tohen and Baldessarini, 1995)

- Non-psychotic rapid cycling bipolar disorder (Suppes, Phillips and Judd, 1994)

- Parkinson's disease with drug-induced and other concomitant psychosis (The Parkinson's Study Group, 1999; Friedman and Lannon, 1989).

Clozapine benefits have also been demonstrated in individuals with:

- Brain injury (Michaels, et al., 1993)

- Co-morbid schizophrenia and substance use disorder (Green, Zimmet and Strous, et al., 1999)

- Severe borderline personality disorder with aggression and self-abusive behavior (Chengappa, Ebeling and Kang et al. 1999; Benedetti, Sforzini and Colombo, et al., 1998)

Although the studies are limited, clozapine appears to be the best treatment for the polydipsia associated with severe mental illness (Verghese, de Leon and Josiassen, 1996; Canuso and Goldman, 1999).

- Typically, polydipsia is associated with schizophrenia, but it can be found in 5% of hospitalized individuals with other mental disorders (Deb, Bramble and Drybala et al., 1994; Bremmer and Regan, 1991; Hayfron-Benjamin, Peters and Woodhouse, 1996).

- In polydipsic patients with schizophrenia, the polydipsia response to clozapine appears to be independent of the antipsychotic response (Verghese, de Leon and Josiassen, 1996).

- Polydipsia can be complicated by hyponatremia, which can be potentially lethal (de Leon, Verghese and Tracy, et al., 1994).

The use of clozapine among individuals with intellectual disabilities is becoming increasingly accepted due to efficacy and safety profiles similar to those reported among non-intellectually disabled individuals.

- Since the early 1990's, several retrospective analyses (Antonacci and de Groot, 2000; Buzan, Dubovsky and Firestone, et al., 1998), case reports/series (Gobbi, 2001; Sajatovic, Ramirez and Kenny et al., 1994; Cohen and Underwood, 1994; Pary, 1994) and single blind studies (Hammock, Levine, and Schroeder, 2001) have shown that clozapine treatment improved psychotic symptoms, self-injurious behavior (SIB), aggression, destruction and stereotyped behavior at relatively low doses.

- A few double-blind placebo-controlled studies (Hammock, Schroeder, and Levine, 1995; Schroeder, Hammock and Mullick, et al., 1995) have confirmed clozapine's benefits in this population.

- These benefits were observed in the full range of intellectual disability and without evidence of increased risk of side effects (at doses under 600mg/d) or decline in cognitive processes.

- Studies showed that 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 per 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 other psychiatric diagnoses (Buzan, et al., 1998).

- Some reports have suggested greater efficacy for clozapine than other SGA agents (e.g. risperidone) as evidenced by progressive improvement in symptoms during the length of the trial (Gobbi, 2001).

Case reports also suggest that individuals with autism and complicated polydipsia may respond to low dose clozapine (<300mg/day) as schizophrenic polydipsic patients do (de Leon, 2003a).

Finally, it should be noted that the U.S. Food and Drug Administration has given clozapine a specific indication for suicidality, based on multiple studies indicating an approximately 5-fold reduction in suicide rates among individuals with schizophrenia and schizoaffective disorder.

Data from the CATIE trials (McEvoy JR, Leiberman JA, et al, 2006) also should be noted as tending to confirm clozapine's antipsychotic superiority to other antipsychotic medications.

Side effects:

Severe neutropenia: Severe neutropenia is the most serious side effect of clozapine and the negative perception of this risk has limited clozapine's use.

Agranulocytosis, defined as an absolute neutrophil count (ANC) of less than 500 cells/mm^3, is estimated to occur in individuals receiving clozapine at a cumulative incidence of 1.3% at one year (Novartis Pharmaceutical, 2003).

- This estimate is based on the occurrence of cases in the US during the clinical testing of clozapine prior to domestic marketing.

- If caught early, severe neutropenia is usually reversible with discontinuation of clozapine treatment.

- Some cases of severe neutropenia have progressed in spite of detection and clozapine discontinuation and some individuals have died.

As of August 21, 1997, under a weekly blood monitoring system, 585 cases of agranulocytosis had been detected in the US out of 150,409 individuals receiving clozapine; 19 cases were fatal (Novartis Pharmaceutical, 2003).

- After 5 years of experience with the CNR, the most recent estimates suggest a cumulative rate of 0.9% (Alvir, Lieberman and Safferman, et al., 1993).

- The risk seems to peak by the third month and declines significantly after the sixth month but never reaches zero (Alvir, et al., 1993).

- This finding led to the WBC monitoring decrease to biweekly after 6 months and to monthly after one year of clozapine therapy.

Agranulocytosis risk appears to increase with age and to be higher in women than in men (Lieberman, Yunis and Egea, et al., 1993).

Safeguards to manage the risk of agranulocytosis, such as registration through CNR clozapine National Registry, 2004) and the requirement for weekly drug monitoring during the first six months of therapy and drug dispensing resulted in lowering the incidence of this condition.

Severe neutropenia is potentially fatal and considered a medical emergency. The best approach to prevent it is careful monitoring. If severe neutropenia develops, clozapine should be discontinued, and the individual should be hospitalized for specialized treatment in an appropriate setting.

Myocarditis and Cardiomyopathy: Myocarditis is a rare and potentially fatal adverse effect of clozapine treatment (Kilian, Kerr and Lawrence, et al., 1999).

- The risk may be highest during the first month of therapy, but it continues as long as the drug is administered (Novartis Pharmaceutical, 2002; Wooltorton, 2002).

- On Feb 20, 2002, Novartis strengthened the box warning regarding the risk of clozapine-associated myocarditis based on post-marketing surveillance data, which revealed 30 reports of myocarditis with 17 fatalities in 205,493 U.S. patients (August 2001).

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.

Clozapine treatment may be associated with the development of cardiomyopathy.

- The risk may be at least 5 times greater than that in the general population (Kilian, et al., 1999).

Any individual in whom myocarditis is suspected should be admitted to an acute care hospital for observation and treatment with corticosteroids, if necessary. Individuals with clozapine-induced myocarditis should not be re-challenged with clozapine.

Seizures: Clozapine-associated seizures are estimated to occur at a cumulative incidence of approximately 5% (Novartis Pharmaceutical, 2003) and appear to be related to dose and rate of titration (Miller, 2000; Novartis Pharmaceutical, 2003; Iqbal, Rahman and Husain, et al. 2003).

Seizure risk should be carefully considered in those with intellectual disabilities, especially in the severe to profound intellectually disabled range.

- Although clozapine treatment increases the seizure risk, none of the studies that we reviewed in this group of individuals has revealed an increased risk.

- However, the dose of clozapine used in these studies appears to be 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.

The interpretation of electroencephalogram (EEG) findings in individuals taking clozapine is confounded by the occurrence of abnormalities in healthy volunteers taking very low doses of clozapine (Iqbal, et al., 2003).

If an individual taking clozapine develops an isolated seizure, this is not a reason for discontinuation of clozapine, but may be a reason to initiate antiepileptic treatment with valproic acid or levetiracetam (Iqbal, et al., 2003).

- If seizures persist, a neurology consultation should be obtained.

Metabolic Complications: Weight gain is well-documented in clozapine treatment.

- Possible mechanisms include antagonism of 5-HT2C and H1 receptors (Wirshing, Boyd and Meng, et al., 2002).

- Different studies have reported varying incidence of weight gain (Miller, 2000) with reports of mean increases of 5.3 to 6.3 kg (11.8 to 14.0 lbs) and substantial percentages of individuals gaining more than 20% of their initial body weight during the first year of treatment (Meyer, 2001).

- Weight gain appears to be linked to clinical improvement (Miller, 2000) and the risk seems to increase with the duration of treatment, especially during the first 4 years of treatment (Henderson, Cagliero and Gray, et al., 2000).

Several studies (Allison, Mentore and Heo et al, 1999; Henderson, et al, 2000; Gianfrancesco, Grogg and Mahmoud et al. 2000; Wirshing, et al. 2002) have highlighted the increased risks of hyperglycemia, lipid abnormalities and diabetes mellitus (types I and II) in individuals receiving clozapine and other SGA medications.

Subsequently, in September 2003, the FDA issued a class labeling change regarding the risks of hyperglycemia and diabetes mellitus in association with SGA medications (FDA letter, 2003).

Whether changes in glucose and lipid metabolism depend entirely on the presence of weight gain is only partly known. While weight gain and metabolic abnormalities correlate with each other, it is likely that they are somewhat independent (Wirshing, et al., 2002).

- Epidemiological studies have suggested an increased risk of hyperglycemia-related adverse events in individuals treated with SGA. However, the precise risk estimates are not available (FDA letter, 2003).

- Reports indicate relatively high rate of new-onset diabetes during treatment with clozapine ranging from 12% (Hagg, Joelsson and Mjorndal, et al., 1998) to 36.6% (Henderson, et al. 2000).

- Confounding factors include an increased background risk for diabetes in individuals diagnosed with schizophrenia as well as lack of physical activity, dietary intake and an African American ethnicity.

- Despite these factors, clozapine treatment by itself appears to carry an increased risk for diabetes mellitus.

- Mechanisms other than obesity may be involved in clozapine-associated type II diabetes.

- The possible mechanisms involved include suppression of insulin release, insulin resistance, or impairment of glucose utilization. (Henderson, et al., 2000).

Weight gain is best managed with dietary interventions (nutritional consultation and dietary regimens) and exercise.

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.

- *The most useful pharmacological intervention in preventing weight gain and metabolic abnormalities has been metformin*.

Clozapine treatment has been associated with elevated triglyceride levels (Henderson, et al. 2000; Wirshing, et al., 2002; Ghalei and Dufresne, 1996; Meyer, 2001), which is an independent risk for coronary atherosclerosis.

- The mechanisms of clozapine-associated hyperlipidemia are largely unknown.

Orthostatic changes and tachycardia. Orthostatic changes and tachycardia can be avoided by careful monitoring and delaying titration to allow the individual to develop tolerance.

- 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).

- Rising slowly from the sitting or the lying position and increasing fluid and salt intake are advised.

- Support stockings and tilting the head of the bed at night may be needed.

- Pharmacological management with fludrocortisone may be indicated for some individuals.

Tachycardia is a rather common side effect of clozapine treatment, occurring in about 25% of cases (Miller, 2000).

- Tachycardia 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.

- Persisting tachycardia > 110 bpm is a risk factor for later cardiomyopathy.

- Some data indicate that risk begins to increase at resting heart rates > 80 bpm.

- Persisting tachycardia can be treated with low-dose atenolol.

- In some cases, tachycardia may be indicative of myocarditis.

Fever: The presence of fever and/or infection may be indicative of the presence of agranulocytosis.

- However, most cases of fever in clozapine receiving individuals 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, occurring in up to 5% of individuals, usually within the first three weeks of treatment.

- It typically involves minor increases of 1 – 2 degrees F and resolves spontaneously with continuation of treatment (Safferman, Lieberman and Kane, et al., 1991).

Sedation. Sedation is the most common side effect of clozapine treatment (Miller, 2000, Novartis Pharmaceutical, 2003).

- It is reported to occur in 39% of cases (Novartis Pharmaceutical, 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; 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 stimulant should be considered with caution due to the risk of worsening psychosis (Iqbal, et al., 2003).

Constipation: Clozapine has strong anticholinergic effects, and thus can cause significant constipation.

- 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.
- Secretogogues may be beneficial for chronic constipation in clozapine-treated individuals.
- For persons with a history of fecal impaction, ileus, or bowel adhesions, routine monitoring via KUB is often prudent.
- Clozapine has caused bowel obstruction leading to death and this is a *more common cause of mortality than agranulocytosis*.

Hypersalivation: Hypersalivation may be the second most common effect of clozapine treatment. It commonly occurs at night.

- Most antimuscarinic drugs cause dry mouth; however, clozapine frequently causes hypersalivation.

- Clozapine is an antagonist at M3 (most muscarinic receptors) and an *agonist at M4 receptors*.

- The M4-agonist properties have been associated with clozapine-induced hypersalivation.

- IMPORTANTLY, *norclozapine* (a.k.a., desmethyl-clozapine, the metabolite of clozapine) is an *agonist at all of the muscarinic receptors* and may be the primary culprit in promoting sialorrhea (de Leon, Odom-White and Josiassen, et al., 2003).

- Other authors have hypothesized that blocking of alpha-receptors may be a contributing factor (Marder and Wirshing, 2004).

- Hypersalivation typically occurs at night. Individuals are recommended to sleep with a towel on the pillowcase to prevent soaking the pillow at night.

- A number of pharmacological agents have been employed based on case reports or open label studies.

- These include anticholinergic drugs such as oral benztropine mesylate (Reinstein, Sirotovskaya and Chasanov, et al., 1999); sublingual ipratropium spray or 1% atropine drops (Townsend and Baier, 2004); scopolamine patches (Gaftanyuk and Trestman, 2004); or alpha-decreasing central agonist agents, such as clonidine patches (Grabowski, 1992).

- The side effect profiles of these agents must be considered (e.g. constipation/bowel obstruction/paralytic ileus associated with benztropine or glycopyrrolate and clonidine-induced hypotension).

- Chewing gum can be used in combination with benztropine mesylate (Iqbal, et al. 2003).

- Simple dose reduction in stabilized individuals may reduce hypersalivation.

- Generally, systemic anticholinergic medications should be avoided in combination with clozapine.

- Alternatives include topical anticholinergic agents such as atropine drops or ipratropium spray or botulinum injections of the salivary glands.

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 (e.g. ephedrine, an alpha-adrenergic agent, and oxybutynin, an anticholinergic agent have been successfully used (Iqbal, et al., 2003).

- Vasopressin or anti-diuretic hormone analogs such as DDAVP also have been used.

Myoclonic Jerks: Myoclonic jerks, particularly manifested as orofacial movements (Bak, Bauer and Scaub, et al., 1995), knee buckling or leg folding (Antelo, Stanilla, and Martin-Lionch, 1994) may occur during clozapine treatment.

- 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 and Kasper, 1993).

- Clozapine dose reduction or anticonvulsant use may be needed for management.

Extrapyramidal Effects: Unlike FGA medications, clozapine is relatively free from certain motor side effects such as parkinsonism and akathisia and there have been no confirmed association with tardive dyskinesia.

- In fact, there is some evidence that clozapine treatment may effect improvement in antipsychotic-induced tardive dyskinesia, parkinsonism and chronic akathisia (Spivak, Mester and Abesgaus, et al., 1997).

- The low risk of drug-induced tardive dyskinesia during clozapine treatment has particular promise for individuals with intellectual disabilities because of the relatively high risk (20-80%) of antipsychotic-induced dyskinesia in this group of individuals (Sajatovic, et al., 1994).

- In addition, reports of benefits in improving some aspects of cognitive and social functioning in individuals makes clozapine use, when properly indicated and monitored, an attractive option for individuals with cognitive impairments.

Delirium: Clozapine treatment has been implicated in the development of delirium or confusion in the elderly or individuals with cognitive deficits (Young, Bowers and Mazure, 1998), probably due to its anticholinergic and sedating properties.

- Consequently, medications with anticholinergic effects and CNS depressants can increase this risk and they should be used with caution in individuals taking clozapine.

- Dose reduction and slowing the rate of titration may be needed if delirium occurs.

- On the other hand, some cases of delirium were attributed to clozapine withdrawal (Stanilla, de Leon and Simpson, 1997) and they resolved after clozapine was restarted (Iqbal, et al., 2003).

Other side effects: Dizziness occurs in more than 10% of cases.

Relatively frequent side effects (1-10%) also include:

- Cardiovascular (hypertension, syncope)

- CNS (tremors, ataxia, slurred speech)

- Gastrointestinal (heartburn, nausea, vomiting)

- Hematological (eosinophilia, leukocytosis)

- Hepatic (abnormal liver function tests)

- 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 (Novartis Pharmaceutical, 2003; Miller, 2000; Iqbal et al., 2003).

- Of interest, clozapine-associated NMS may lack the rigidity associated with the classic syndrome.

Usage:

Dosage: In the U.S., clozapine is used up to 900 mg/day in adults.

- Rarely, patients have required higher doses to reach therapeutic levels.
- Nevertheless, *clozapine plasma concentrations are a better guide to treatment adequacy than dose*.
- Optimal plasma concentrations for most patients is 350 to 600 ng/ml, with some more treatment-resistant patients requiring plasma concentrations of circa 1,000 ng/ml (Bender and Eap, 1998).

Blood levels: Several controlled clozapine level studies have been conducted in treatment-resistant schizophrenia.

- Most studies recommend plasma clozapine therapeutic concentrations higher than 350 ng/ml, with some patients needing plasma concentrations of circa 1,000 ng/ml (Perry, Miller and Arndt et al. 1991; Hasegawa, Gutierrez-Esteinou and Way, et al., 1993; Kronig, Munne and Szymanski, et al., 1995; VenderZwaag, McGee and McEvoy, et al., 1996)
- Some researchers identified 420 ng/ml as the minimum antipsychotic threshold (Potkin, Bera and Gulaskaram, et al., 1994).
- Some of the cited studies found that plasma concentrations above 600 ng/ml were associated with an increased side-effect burden.

5 basic principles need to be considered to interpret clozapine blood levels:

1. Standardization:

    a. 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 hours after the last dose.

    b. A steady state level is usually estimated to require 5-6 half lives.

c. The elimination half-life of clozapine, which is reported to be shorter than that of FGA, is estimated to be 14.2 hours with a range of 6-33 hours. The rounded average of the half-life is 24 hours (de Leon, Henighan and Stanilla, et al., 1996).

   Thus, a good rule of thumb 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).

d. One needs to be sure of adherence with treatment during the week prior to obtaining levels.

   When an abnormally low level is observed, one should first suspect nonadherence (common) and rapid metabolism next.

2. Parent versus metabolite levels:

   a. Most clozapine level studies also measure concentrations of norclozapine (a.k.a. N-desmethyl-clozapine), the primary metabolite of clozapine.

   b. 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, especially sialorrhea (de Leon, et al., 2003a).

   c. Thus, although norclozapine levels may assist in monitoring clozapine metabolism (de Leon and Diaz, 2003) they do not seem to predict therapeutic response.

3. Therapeutic window:

   a. The width of the therapeutic window determines the clinical significance of changes in plasma levels.

   b. The lower limit of the window is the lowest level that is associated with therapeutic efficacy. The lower limit of the window is 350 – 420ng/ml.

   c. The upper limit is the level above which toxicity occurs. Levels higher than 1, 000ng/ml have been associated with toxicity, including seizure risk and severe sedation (Simpson and Cooper, 1978).

d. Compared to other SGA, clozapine has a much narrower therapeutic index (de Leon, 2004a).

4. Normal variations:

a. Clinicians frequently fail to understand that a single clozapine level must be cautiously considered and that a pattern change in several levels is more easily interpreted.

i. Even after assuming stability of all possible confounding factors (e.g., timing of collection, dose and schedule, and drug interactions), laboratory, technical, and natural variations can cause some day to day variations in clozapine levels.

b. There is limited information on normal variations of clozapine levels seen in the naturalistic setting (Kurz, Hummer and Kemmler, et al., 1998; de Leon and Diaz, 2003).

i. 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).

ii. This means that if an individual has a clozapine level of 500ng/ml, the next one in the same stable conditions should not be > 1000ng/ml or < 250ng/ml.

iii. However, a change from 500ng/ml to 400ng/ml is probably not very significant unless it is part of a trend.

5. Relationship between dose and level:

a. In typical doses, clozapine appears to have a linear relationship between typical doses and concentrations (first order kinetics) (Choc, et al. 1987), particularly within the same individual.

i. Pharmacologists use a simple formula, the concentration to dose ratio or C/D (de Leon, 2004b) to represent this relationship.

b. Plasma clozapine concentrations exceeding 350ng/ml are described as therapeutic, with most individuals requiring a dose of 300-600mg/day to reach these levels.

i. Assuming that each individual needs a dose of 300 mg/day to reach a level of 350ng/ml, this provides a C/D 1.2 (350/300).

ii. Conversely, assuming that each individual needs a dose of 600mg/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.

c. Individuals requiring higher clozapine doses to reach therapeutic concentrations have a lower C/D.

i. For example, one individual thought to have a high capacity to metabolize clozapine had a C/D <0.17 (Bender and Eap, 1998).

d. In summary, it appears that the average individual may need at least 300 mg/day to reach a therapeutic level (Simpson, et al. 1999). C/D has implications for dose titration, which will be discussed later.

Clozapine metabolism:

- The clozapine dosing recommendations provided by package labels are generated by the dose response of the "average subject" in the double-blind studies where most co-prescriptions are forbidden.

- Therefore, these recommendations may not be appropriate for many real-world individuals who cannot be considered "average" (e.g., individuals lacking or having too much of the enzyme responsible for clozapine metabolism, and/or individuals taking other medications that significantly influence the metabolism).

- Approximately 70% of clozapine metabolism is explained by the cytochrome P450 1A2 (CYP1A2) (Bertilsson, Carrillo and Dahl, 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).

Genetic factors:

- Until very recently, no individuals lacking CYP1A2 (poor metabolizers) were described.

- A few individuals having too much CYP1A2 (rapid metabolizers) have been reported (Bender and Eap, 1998).

- Current knowledge suggests that it is very unlikely (<1%) that polymorphic genetic variations may explain unusual clozapine levels.

Significant drug interactions:

Drug interactions may be important determinants of clozapine doses and levels.

The following is an outline of significant drug interactions that physicians prescribing clozapine need to consider:

Anticonvulsants:

- Available information indicates that *valproic acid is probably the anticonvulsant of choice in individuals taking clozapine*, as 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).
- Three “old” anticonvulsants, phenobarbital, primidone and phenytoin, are powerful clozapine metabolism inducers (de Leon, 2004b).
    - Although there is limited available information, one should expect that an individual taking phenytoin may need doses four times higher than would be needed if not taking phenytoin (Miller, 1991).
    - The inductive effects of these drugs may typically take two to three 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 two to three 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.
- Gabapentin, levetiracetam, topiramate and tiagabine are probably free of drug interaction with clozapine.
- It is not yet clear if lamotrigine interacts with clozapine.

Antidepressants:

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

- Most serotonin selective reuptake inhibitors (SSRIs) appear to be metabolic inhibitors.

    - Fluvoxamine, in particular, is a very strong inhibitor of CYP1A2 (Hiemke, Weigmann and Harter et al. 1994).

    - Fluvoxamine has been used to lower clozapine dose for economic reasons, but it appears safer to avoid it.

    - Similarly, sertraline (Pinninti and de Leon, 1997), fluoxetine (Centorrino, et al. 1994) and paroxetine may moderately increase clozapine levels.

    - 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, mirtazapine, levomilnacipran and bupropion.

Mood stabilizers:

- As described above, valproic acid is unlikely to cause major interactions.

- Lithium does not change clozapine levels and has been used to increase ANC in individuals taking clozapine.

- Carbamazepine should be avoided due to the risk of severe neutropenia.

- Although oxcarbazepine carries a substantially lower risk of blood abnormalities than carbamazepine, it should probably be used with caution.

Antipsychotics:

- Although only limited data supports this practice, clinicians sometimes prescribe antipsychotics to augment clozapine response.

- One should consider the effects of added blocking of brain receptors, as many antipsychotics block the same dopaminergic, adrenergic, serotonergic, muscarinic and histaminic receptors involved with clozapine.

- Some antipsychotics may increase clozapine levels.
    - Among the FGA, perphenazine (Cooke and de Leon, 1999) and other phenothiazines clearly have potential to increase clozapine levels.
    - 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 SGA to clozapine. The metabolism of both clozapine and olanzapine is mainly dependent on the same enzymes (CYP1A2 and UDP-glucuronosyltransferases) (de Leon, 2003b).
    - Thus, one should assume that clozapine can increase olanzapine levels and, even more worrisome, 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.
    - Although there are no data, it is reasonable to expect that quetiapine and aripiprazole are unlikely to increase clozapine levels.
    - Ziprasidone should not increase clozapine levels.
    - No systematic data exist regarding asenapine, iloperidone, or lurasidone.

<u>Benzodiazepines:</u>

- A poorly understood benzodiazepine interaction with clozapine has been described in a few individuals during the first days of clozapine treatment, usually within 24 to 48 hours after the first clozapine dose.
- Side effects of this interaction may include lethargy, ataxia, loss of consciousness, and, rarely, respiratory arrest.
- There were 7 cases of respiratory arrest after treating 12,000 US individuals, but only 2 of these cases were associated with the combination of benzodiazepines and the first clozapine doses (Finkel and Schwimmer, 1991).

- Of 162 individuals treated with the combination of clozapine and benzodiazepines in a German hospital, one death due to respiratory arrest occurred in an individual suffering from liver impairment (Klimke and Kleiser, 1994).

- The occurrence of respiratory arrest during the co-administration of benzodiazepines and clozapine appears to be an idiosyncratic reaction many individuals tolerate this combination, even in the first days of clozapine treatment, without any obvious side effects.

- However, it is safer to avoid benzodiazepines the week before starting clozapine and during the first week of dose titration.

Other medications:

- The fluroquinolones, particularly ciprofloxacin and norfloxacin, are powerful CYP1A2 inhibitors and are expected to increase clozapine levels (Raaska and Neuvonen, 2000).

    - Other fluroquinolones, 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 (Hagg, et al., 1999), close monitoring is recommended when adding to clozapine.

- Cimetidine should be avoided in individuals taking clozapine (Szymanski, Lieberman and Picou et al. 1991).

- Omeprazole can lower clozapine plasma levels significantly; therefore, another proton pump inhibitor should be chosen.

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 (Vistisen, Loft and Poulsen, 1991), and may mildly reduce clozapine levels but clinical significance is unlikely.

- Although grapefruit juice does not appear to inhibit clozapine metabolism, it should not be administered to individuals 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, Diaz and Rogers, et al., 2003b).

    - However, only high caffeine intake may have clinically significant interactions with clozapine.

    - In the US, brewed coffee is estimated to contain 85mg/5 oz cup; instant coffee, 65mg/5 oz cup; decaffeinated coffee, 3mg/5 oz cup; tea, 40 mg/5 oz cup; and caffeinated sodas including caffeinated colas, 40mg/12 oz can (or one sixth of a 2 liter bottle) (de Leon, et al. 2003b).

    - Caffeinated over-the-counter medicines may have a lot more caffeine in a pill (up to 200mg).

    - There are no data on what level of caffeine intake is safe for individuals taking clozapine.

    - Steady caffeine doses in a stabilized clozapine individual 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 data defines what a “dramatic” change is, caution has been recommended with increases or decreases of daily caffeine intake of >1 cup of coffee (or 2 cans of caffeinated sodas) in non-smokers and >3 cups (or 6 cans of caffeinated soda) in smokers.

- For example, when a smoker taking clozapine increases caffeine intake by 3 coffee cups (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 2 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).

Smoking tobacco:

- Tobacco smoking byproducts, particularly the polycyclic aromatic hydrocarbons, are metabolic inducers that lower clozapine plasma levels.

- Similarly, if a non-smoking individual starts to smoke heavily (>one pack/day), the clinician may need to consider increasing the clozapine dose by a factor of one and a half over two to four weeks.

    - Since 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 inductive effects take at least 2 to 4 weeks to disappear (Zullino, Delssert and Eap, et al., 2002; Skogh, Bengtssson, and Nordin, 1994; McCarthy, 1994).

    - Smoking cessation would probably cause clozapine levels to increase by a factor of 1.5 at circa 2 to 4 weeks later.

- Checking for side effects and measuring a clozapine level may then be prudent since the one and a half factor is a gross approximation (de Leon, 2004a).

- It appears that gender may play a role.

    - The limited available information suggests that an average female non-smoker may require clozapine doses around 300mg/day to reach therapeutic levels, while an average male heavy smoker may require high doses (around 600mg/day).

    - Male non-smokers and female smokers fall in between (Perry, Bever and Arndt, et al., 1998; Rostami-Hodjegan, Amin and Spencer, 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.

Respiratory infections:

- Respiratory infections can inhibit CYP1A2 because cytokines released during infection decrease the enzyme activity and synthesis (Abdel-Razzak, Loyer and Fautrel et al. 1993).
- Clinicians caring for individuals taking clozapine must be careful should the individual develop serious respiratory infections with fever and pay special attention to signs of toxicity including severe sedation, myoclonus or even seizures.
- If any of these signs appear, they need to decrease clozapine dose at least by half, until the individual has recovered from the infection (de Leon, 2004c).

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