CLINICAL PROFILE OF CLOZAPINE: ADVERSE REACTIONS AND AGRANULOCYTOSIS

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The arrival of clozapine has been one of the most significant developments in antipsychotic drug treatment since the advent of chlorpromazine ushered in the psychopharmacologic era. However, its utilization has been significantly limited and complicated by its potential to cause adverse effects and agranulocytosis in particular. It must be emphasized that clozapine has a side effect profile that is in many ways distinct from standard typical antipsychotic drugs. Side effects with clozapine are common and range from the benign to the potentially lethal. The most common side effects include sedation, dizziness, and sialorrhea during sleep; the most serious are agranulocytosis, seizures and respiratory depression. Although side effects from clozapine are not necessarily preventable, they are for the most part manageable. Even with the most serious adverse effects, proper knowledge of the medication's actions, clinical vigilance, and prompt intervention can prevent the occurrence of significant morbidity and mortality as a consequence of clozapine treatment.

INTRODUCTION

The advent of clozapine has been one of the most significant developments in antipsychotic drug treatment since the synthesis of chlorpromazine (1). In preclinical and clinical investigations, it

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was found to have properties that were atypical of classic neuroleptic drugs and offered substantial therapeutic advantages. Clozapine neither causes acute extrapyramidal side effects (EPS) and tardive dyskinesia (TD), nor elevates prolactin (PRL) to the same extent as do classic neuroleptic drugs (2). Moreover, its antipsychotic efficacy was found to be superior to standard neuroleptics in patients whose condition is refractory to treatment (3). It has also been suggested that clozapine might possess efficacy against negative symptom psychopathology and the functional impairment caused by schizophrenia which are less responsive or unresponsive to standard neuroleptic therapy (3–5).

Despite its obvious potential advantages, clozapine has taken almost three decades to become commercially available in the United States, Canada and Great Britain. This was largely due to its potential for adverse reactions and specifically agranulocytosis. It is important to understand that clozapine differs in many ways from standard neuroleptic drugs in its side effect profile, and thus requires different clinical measures to be taken in the management of patients who are receiving it. The consequences of not being aware or vigilant can be serious—and potentially fatal—iatrogenic complications of therapy. The purpose of this paper is to review the spectrum of side effects associated with clozapine treatment, examine their pharmacologic basis and describe methods for their clinical management.

REVIEW OF ADVERSE EFFECTS

The frequency of side effects caused by clozapine is very high in that the majority of patients treated with this medication will experience one or more of its various side effects (6–10). Table 1 lists specific side effects in their order of their observed frequency of occurrence. It should be pointed out that the frequencies listed are estimates based on premarketing data and that the actual rates may be even higher in patient populations. The incidence of side effects reported with the use of clozapine varies widely in some cases due to differences in reporting methods, study design, treatment duration, dosing and titration strategies, definitions for a particular adverse reaction, frequency of monitoring for that particular side effect, and use of concomitant medications.

TABLE 1
Frequently Observed Adverse Reactions Reported with Clozapine

Reaction	%
Drowsiness or sedation	39
Salivation	31
Tachycardia	25
Dizziness	19
Constipation	14
Nausea/vomiting	11
Hypotension	9
Sweating	6
Dry mouth	6
Urinary problems	6
Tremor	6
Fever	5
Weight gain	4
Seizures	3
Akathisia	3
Rigidity	3
Myoclonus	2
Agranulocytosis	1

Modified from Safferman et al., 1991.

Many of the side effects that have been observed with clozapine are clearly understandable in light of it's pharmacologic properties (Table 2). However, other side effects e.g. agranulocytosis, nausea, hyperthermia, could not have been predicted or observed until clozapine was administered to large numbers of patients. As do all classic antipsychotic drugs, clozapine exhibits actions on the dopamine (DA) neuronal systems by virtue of its affinity for DA receptors (11–13). However, in contrast to classic neuroleptic drugs, clozapine appears to have a greater affinity to other DA receptor subtypes (D–1, D–4) relative to its affinity for the D–2 receptor (14,15). In addition, clozapine exerts effects on multiple other neurotransmitters including acetylcholine (muscarinic), serotonin (5–HT2, 5–HT1a,b,c, 5–HT3), norepinephrine (alpha-1, alpha-2, beta), histamine (H–1) and possibly glutamate and GABA (12,16–21).

TABLE 2
Pharmacologic Basics for Clozapine Side Effects

	Effects	
Neurotransmitter	*Pharmacologic*	*Clinical*
Dopamine	D_2 Antagonism	Parkinson's – Dystonia – Akathisia ? TD ? Rebound Psychosis ? PRL ⇑ –
	D_1 Antagonism	Cognitive ?
	DA Agonism	Nausea + ?
Acetylocholine	Muscarinic Antagonism	Tachycardia + Constipation + Diaphoresis + Dry mouth - Delirium + Cognitive ? Urinary Dysfunction +
Norepinephrine	α1, α2 antagonism β Antagonism	Sedation + Hypotension + Akathisia ? Sialorrhea + ?
Histamine	H-1 Antagonism	Sedation +
Serotonin	5-HT2 Antagonism 5-HT1a,b,c Antagonism ? 5-HT3 Antagonism ?	Hyperthermia + ? Nausea + ? Myoclonus + ?
GABA	Antagonism ?	Seizures + ?

Pharmacologic properties that are believed to cause the clinical side effects of clozapine. The + sign designates effects that do occur; the – sign indicates effects that would be caused by a particular pharmacologic effect but are not seen (to a significant extent) with clozapine; the ? indicates that the side effect is questionably attributed to that pharmacologic property.

The occurrence of side effects from clozapine is most common during the initiation of treatment and during the acute treatment and dose titration phases. Once stabilized on an effective and tolerable dose of medication, treatment generally proceeds uneventfully as the large number of patients worldwide who have been safely treated with clozapine for many years attests.

HEMATOLOGIC EFFECTS

Clozapine can produce various hematologic effects the most serious of which is agranulocytosis. Agranulocytosis is usually defined as a granulocyte count < 500/mm3, and neutropenia as neutrophil count < 1000/mm3, while leukopenia is defined as a WBC of < 3,500/mm3. The incidence of clozapine associated agranulocytosis has been reported to vary between 0.5% and 2% (22–24), and is generally acknowledged to be substantially higher than occurs with standard antipsychotic and other psychotropic drugs (25,26). One hundred and forty nine agranulocytosis cases had been reported worldwide by 1990 of which 49 had been fatal (27). Most of the deaths from agranulocytosis occurred prior to 1977, before the dimensions of the problem had been recognized and stricter methods for hematologic monitoring were implemented.

In the United States 91 cases of agranulocytosis had occurred through April, 1991 (28,29). Eighteen of these were during the premarketing period, and 73 occurred since clozapine began to be commercially distributed. From the period 2/90 to 5/92 there have been 132 cases of agranulocytosis in the U.S. In addition, there have been at least seven fatalities due to clozapine-induced agranulocytosis in the U.S. while the other cases have recovered without reported medical sequelae (30, Personal communication J. Schwimmer). The fatalities in these cases occurred despite adherence to the weekly blood monitoring system requirement. Deaths occurred due to complications secondary to infections that arose during the course of agranulocytosis. A recent analysis of the U.S. incidence of agranulocytosis on 11,555 patients who received clozapine in the postmarketing period revealed a cumulative rate of 0.8% (95% confidence intervals = .61, .99) at 52 weeks of treat-

ment and 0.91% (95% C.I. = .62, 1.2) at 78 weeks of treatment (this reported incidence is lower than the previous estimate of 1–2%) (28). Older patients and females were at greater risk for developing agranulocytosis. This is consistent with studies of other drug induced blood dyscrasias which found increased rates in older patients and females (31,32). Another potential risk factor that had previously been reported was ethnic status. Lieberman et al (33) found that the incidence of agranulocytosis was increased in patients of Ashkenazi Jewish ancestry. However, these results were based on a small number of patients and must be confirmed. These interesting results have raised the possibility that there is an immunogenetic basis to the vulnerability to develop agranulocytosis with clozapine. Another study involving non-Jewish patients in Europe did not find an association between HLA alleles and clozapine-induced agranulocytosis (34). However, if the HLA haplotype B38, DR4, DQw3 is firmly established as a risk factor for clozapine-induced agranulocytosis in Ashkenazi Jews, then it may be useful to employ pretreatment HLA typing to this patient group.

The natural history of clozapine-induced agranulocytosis has been predominantly, although not invariably, uniform. Over 95% of all cases have arisen in the first 24 weeks of treatment (28,29). However, some cases have arisen after longer periods of exposure (35,36). Therefore, it appears that although the period of maximum risk is in the first six months of treatment with the risk subsequently declining, it does not decline to zero. The mode of onset of agranulocytosis, in most cases, has been gradual, often extending over a period of weeks (28,35,36). However, in a minority of cases it has developed precipitously and within a period of one week or less. The recovery process has similarly been uniform for the most part. Affected patients usually have recovered medically and hematologically within 14 to 24 days depending on the severity of the agranulocytosis (37) and whether it is complicated by sepsis.

Clozapine's hemotologic toxicity appears to be selective for the granulocyte precursors to polymorphonuclear leukocytes with other cell lines being unaffected (30,36). One exception was a fatal case reported by Gerson et al (30) in which anemia, thrombocytopenia and a generally hypoplastic bone marrow were observed. However, the case was unusual in that the patient had a prior history of anemia and had received multiple concomitant

medications including carbamazepine. No cases of aplastic anemia have been reported, and there appear to be no hematologic sequelae following recovery. As a consequence it has been recommended that carbamazepine not be administered concurrently with clozapine as the combination may have additive cytotoxic activity (37). In addition, carbamazepine causes a relatively high incidence of benign neutropenia. This would make it very difficult for the physician to determine if the neutropenia was related to clozapine or carbamazepine and therefore may lead to unnecessary discontinuation of clozapine.

Records of nine patients who developed agranulocytosis with clozapine and were then retreated with clozapine following hematologic recovery were reviewed by Lieberman et al (28) and Safferman et al (38). All of the patients redeveloped agranulocytosis and eight of nine patients did so more rapidly (in approximately 50% less time) than the original episode. This strongly suggests that patients who develop agranulocytosis from clozapine should not be re-exposed to the drug. These observations also have implications for the mechanism by which clozapine produces agranulocytosis. In this instance the evidence would imply that an immune-mediated mechanism is at least partly responsible.

It is clear from the current body of information that clozapine-induced agranulocytosis cannot be prevented from developing. However, fatalities from the complications can usually be prevented. Thus, the risk to patients can be minimized with early recognition of agranulocytosis, immediate discontinuation of clozapine treatment and supportive management. In addition, there is evidence that recovery from clozapine-induced agranulocytosis may be accelerated by the administration of Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) and Granulocyte-Colony Stimulating Factor (G-CSF) (39,40). Further study will be necessary to determine how to use these myeloid growth factors in the most effective fashion.

Hematologic monitoring should be geared to providing optimal safety in the most clinically efficient manner. The guidelines of monitoring systems vary in different countries and are still being evaluated. It is recommended that a complete differential white blood cell count be obtained in addition to the total white blood cell count on a weekly basis as there have been reports of neutropenia occurring with a normal total white blood cell count (41).

It goes without saying that the identification of the mechanism of clozapine-induced agranulocytosis would be of enormous value. There are two possible pathophysiologic mechanisms which are currently being investigated. One is that clozapine, and/or one of its metabolites, has direct toxic effects on the granulocyte precursors in the bone marrow and peripheral circulating leukocytes; or alternatively that drug administration leads to the development of an antibody directed against the bone marrow granulocyte precursors and peripheral leukocytes. (For detailed reviews of these mechanisms see 25,26,37,42–44). In addition, some investigators have found in vitro evidence that activation of neutrophils may lead to the formation of clozapine metabolites that exist as free radicals and in this way produce agranulocytosis (43). The authors suggest that the coadministration of ascorbic acid (Vitamin C), a reducing agent, may prevent clozapine-induced agranulocytosis by reducing these free radicals. Although the question is far from being answered, the current evidence suggests that an immune process underlies clozapine induced agranulocytosis (45).

Clearly, the identification of risk factors for and the pathogenic mechanism of clozapine induced agranulocytosis would have important benefits for patients in terms of increased safety and reduced cost of treatment. Perhaps most importantly, such findings could lead to broadening the population who could potentially receive treatment with clozapine.

Other hematologic changes that have been described with clozapine include leukocytosis (0.6%) (36), eosinophilia (1%) (46,47), and leukopenia/neutropenia/decreased WBC (3%) (48), thrombocytopenia (30,49), and mild anemia (37).

Guidelines and parameters for the management of a drop in the WBC have been published by the manufacturer (48). Any fever or sign of infection (i.e. pharyngitis) is an immediate indication for a WBC count with differential especially within the first 18 weeks of treatment. If the patient has a WBC count below 2000 or a granulocyte count below 1000 clozapine must be discontinued. It is also suggested that patients with WBC levels below 3,500 not receive clozapine because of the difficulty that would be involved in the early identification of agranulocytosis. However, further study of patients who normally have low WBC levels or with benign idiopathic neutropenia are warranted so as not to exclude unnecessarily patients and populations in whom this occurs. There is no

compelling evidence that patients who normally have low neutrophil counts are at an increased risk of developing clozapine-induced agranulocytosis. Some investigators have successfully treated such patients with clozapine by pretreatment with lithium carbonate to raise neutrophil counts to a more comfortable level. However, it is clear that lithium carbonate, a weak stimulator of neutrophil production, cannot prevent clozapine-induced agranulocytosis and therefore should not be used for that purpose.

CENTRAL NERVOUS SYSTEM EFFECTS

Behavioral

Sedation is the most prevalent CNS effect of clozapine (7,48). Almost all patients will sustain the sedating effects of clozapine at the initiation of treatment but they will rapidly develop tolerance in the context of gradual dose escalation so that sedation ceases to be a limiting factor. A small proportion of patients may continue to experience some measure of clozapine's sedating effects. This may be reduced or alleviated by consolidation of dosing at H.S. or by dose reduction. Sedation, possibly associated with hypotension, may be experienced by patients as dizziness. Clozapine's antihistaminic and antiadrenergic properties may be at least partly responsible for sedation.

Other behavioral effects that can be caused by clozapine include confusion and, in extreme form, delirium. This can occur in susceptible patients and in the elderly possibly from clozapine's intrinsic anticholinergic properties and/or due to too rapid dose escalation (50). The therapeutic dose range and safety of clozapine in the elderly has yet to be determined and remains an important area for future research.

A recent case report has described the transient emergence of obsessive-compulsive symptoms during clozapine treatment (51). This is interesting from the standpoint of clozapine's potent central nervous system antiserotonergic effects. Studies are needed to accurately determine how prevalent this phenomenon is.

There have been a few reports of rapid return of psychotic symptoms after abrupt discontinuation of clozapine (52–56). While these investigators have linked it to a supersensitivity psychosis (super-

sensitivity of the mesolimbic system) as described by Chouinard et al (57), others question it's existence (58). The phenomenon of rapid relapse observed in some patients may in part be due to the rapid elimination of clozapine and dissipation of its pharmacologic effects following discontinuation relative to standard neuroleptics. When clinical circumstances permit, clozapine should be tapered gradually to avoid withdrawal symptoms such as diaphoresis, diarrhea, restlessness, anxiety, and insomnia.

Neuromuscular

Clozapine can produce a range of neuromuscular effects though not those which are traditionally associated with antipsychotic drugs. Although it can induce tremor (usually fine and fast), clozapine produces virtually no parkinsonian effects (bradykinesia or rigidity) or dystonia. Motor agitation has been described in patients treated with clozapine which some authors have interpreted as akathisia (59). However, it is not clear that this is due to subjective restlessness and associated with subjective discomfort as would be expected in true akathisia. Safferman et al (60) have suggested that patients with preexisting tardive akathisia may have their symptoms released (i.e. no longer suppressed) as they are converted from standard neuroleptic treatment to clozapine and thereby appear to emerge as a consequence of clozapine treatment.

Cases resembling neuroleptic malignant syndrome (NMS) have been reported with clozapine in combination with lithium or carbamazepine (61,62). More recently NMS has been described with clozapine as the sole etiologic agent (63–65). Careful attention must be paid to the spectrum of symptoms that are often seen with clozapine treatment that may be incorrectly diagnosed as a case of NMS. Such side effects may include tachycardia, diaphoresis, fever, leukocytosis, and delirium. Unless rigidity is present the diagnosis of NMS cannot be made with certainty.

Until recently it had been thought that clozapine did not cause tardive dyskinesia (TD). However, Kane et al (66) described two patients who appeared to develop signs of TD after an average of 7.7 years of clozapine treatment. Although the authors believe that the patients did not have TD prior to the initiation of clozapine, they could not be entirely certain since the patients did

have lengthy prior neuroleptic exposure and were converted to clozapine treatment without undergoing a sustained washout. Similarly de Leon et al (67) described a case of jaw dyskinesia that developed during clozapine treatment. As seen in the cases described by Kane et al this patient had received a typical neuroleptic prior to taking clozapine. Thus the question of whether clozapine can cause TD remains open. However, it does seem clear that if there is any TD liability associated with long term clozapine treatment, it is substantially lower than that seen with standard neuroleptic therapy (66). The contention that clozapine can cause TD can only be answered by prospectively treating a large cohort of neuroleptic patients with clozapine.

Seizures

As do many psychotropic medications, clozapine lowers the seizure threshold of patients (68). EEG changes are very commonly associated with clozapine treatment and clozapine's propensity to cause seizures is greater than most commonly used drugs (69). This effect is clearly dose related and may also be in part dependent upon the rate of titration. Various guidelines have been suggested to minimize or manage this risk including: obtaining an EEG prior to raising the dose above 600 mg/day; combining clozapine with anticonvulsants at doses where a seizure occurred before (70), monitoring clozapine blood levels (71); reduction of dose to 50% of dose at which a seizure occurred and obtaining a neurology consult (6). The occurrence of a seizure in a patient need not preclude continued treatment with clozapine. Therapy may continue after a recovery period at a lower dose (50% reduction or more to be safe). Alternatively, anticonvulsant medication may be added to prevent further seizures. Certain anticonvulsants may be preferable to others. For example, carbamazepine is contraindicated for obvious reasons. Phenytoin has been reported to lower the blood levels of clozapine through increased hepatic microsomal enzyme activity (72). Phenobarbital is not favored by neurologists and can also induce hepatic enzymes which may alter clozapine metabolism. Thus, by a process of elimination valproic acid may be the anticonvulsant of choice at least for the time being especially because it may be less likely to affect blood levels of clozapine to the same extent as with phenytoin and others. If the clinician chooses to

discontinue drugs that raise the seizure threshold (e.g. benzodiazepines), this should preferably be done prior to initiating clozapine. If the clinician chooses to discontinue such drugs after clozapine treatment has already commenced, discontinuation should be done very gradually to avoid precipitating seizures.

A small proportion of patients treated with clozapine develop a mysterious and potentially serious neuromuscular phenomenon that has been described as myoclonic jerks or cataplexy (5,6,73). This reaction is characterized by involuntary contractions or loss of muscle tone which can result in a sudden change in body position or posture, or, in the extreme, complete collapse. It is neither associated with stigmata of seizures, eg. auras, incontinence, nor affects the patient's level of consciousness. It is not known if this is peripherally or centrally mediated. At least some cases have been associated with abnormal spike activity on EEG suggesting that these neuromuscular phenomena may have an electrophysiologic diathesis. This adverse reaction can usually be eliminated by reducing the dose of clozapine. If this is not feasible it may be useful to add valproic acid.

CARDIOVASCULAR AND RESPIRATORY EFFECTS

Hypotension and tachycardia are the most frequently occurring cardiovascular effects caused by clozapine (6,8,10,48). Hypotension commonly occurs at the beginning of treatment with its prevalence and severity being significantly influenced by the rate and magnitude of dose titration. It is caused predominantly by the antiadrenergic properties of clozapine. Generally, patients develop tolerance to the hypotensive effects, although they can persist in some patients and be a limiting factor in, not just the rate of dose escalation, but the absolute dose that can be tolerated. Rarely, orthostatic hypotension has occurred with profound collapse and respiratory arrest (10,74,75). There have been at least four cases of respiratory arrest and one case of cardiac arrest which have predominantly occurred at the initiation of clozapine treatment. Two of these patients were concurrently receiving benzodiazepines. It is not clear what the extent of this reaction is, and whether this is a predictable consequence of the drug's pharmacologic properties or idiosyncratic reactions.

Although increases in heart rate may be associated with the hypotensive effects of clozapine, the major cause of tachycardia appears to be its anticholinergic properties and not simply a compensatory response to hypotension (6,8,35). In addition, elevation in plasma norepinephrine caused by clozapine may also be responsible for the tachycardia. Consequently, tachycardia is usually dose related and, although some adaptation in rate may occur with sustained treatment, it may persist throughout treatment. For this reason in cases where the dose of clozapine cannot be sufficiently lowered, the addition of a peripherally acting beta blocking agent e.g. atenolol, may be necessary. Clozapine may also cause repolarization changes as evidenced by flattening or inversion of T-waves on the EKG. This is usually of no clinical significance and is reversible upon dosage reduction or discontinuation. We have also observed a case of clozapine-induced premature ventricular contractions but this appears to be very infrequent (unpublished observation).

GASTROINTESTINAL AND HEPATIC EFFECTS

Clozapine produces a range of G.I. effects including those that are both predictable and paradoxical. Constipation and dry mouth occur as would be expected in view of the potent anticholinergic properties of clozapine but at relatively low rates. However, the most prominent side effect is hypersalivation which occurs to some extent in most patients treated with clozapine and to which tolerance does not develop. This does not appear to be a consequence of sedation, parkinsonism or reduced deglutition which might allow saliva to accumulate. Treating this problem with anticholinergic agents may be effective (9) but will heighten the risk of toxicity and is therefore not recommended routinely (6). We have speculated that different receptors located on salivary glands including adrenergic (alpha and beta) (76), muscarinic (77), and increased concentrations of the tachykinin, substance P (78), can alter salivary flow or composition. It is conceivable that the contribution of alterations in peripheral adrenergic tone and substance P can override the antimuscarinic effects of clozapine at the level of the salivary glands. We and others have successfully managed clozapine-induced hypersalivation with clonidine (an α_2-agonist) (unpublished data, 79).

Similarly, paradoxical is the occurrence of nausea and, in some cases, vomiting by clozapine since all neuroleptic drugs have antiemetic effects by virtue of their D–2 blocking properties. The nausea that patients treated with clozapine experience does not seem to be due to peripheral G.I. effects or bloating due to excessive saliva being swallowed. The nausea appears to be a centrally mediated effect perhaps due to DA and/or 5–HT agonistic effects of clozapine treatment. Despite the fact that clozapine is a DA and 5–HT antagonist, it has been shown to increase presynaptic activity of DA and 5–HT with chronic treatment (2). Thus, increased activity of either or both of these neurotransmitters in the hypothalamus could cause nausea and lead to vomiting. If the clozapine dose can not be reduced, the addition of antacids (aluminum and magnesium hydroxides) is sometimes helpful. Alternatively, one can administer ranitidine (or famotidine). Cimetidine is not recommended because its ability to inhibit hepatic microsomal P–450 enzymes have been associated with significant increases in the blood level of clozapine (80).

Clozapine can produce increases in hepatic enzymes which in most cases are transient. In some patients, however, these can be substantial and sustained leading to a drug-induced hepatitis although usually there are no associated signs or symptoms. This adverse reaction can be managed by suspending treatment or lowering the dose until the condition resolves.

ENDOCRINE

Since clozapine does not elevate prolactin to any degree comparable to standard neuroleptics, it is not associated with galactorrhea and amenorrhea (6,81,82). Clozapine treatment does, however, often lead to weight gain and may even be more prone to cause this side effect that standard neuroleptic drugs (83–85). It has been reported that clozapine may lower plasma cortisol levels in humans (2).

GENITOURINARY

Clozapine infrequently is associated with urinary incontinence usually in the form of enuresis. The pathophysiologic mechanism of this is not known but may be due to overflow incontinence

secondary to the drug's anticholinergic effects, or, alternatively in the case of enuresis, to the deep sleep produced by the sedating effects of the clozapine. As it is a distressing problem which affects the quality of life for some patients, agents such as DDAVP and imipramine have been suggested as urologic treatment. Clozapine can also cause sexual dysfunction in the form of erectile and ejaculatory dysfunction in males, and orgasmic dysfunction in females. Clozapine rarely has been reported to cause priapism (86,87).

PREGNANCY

Experience with clozapine use in pregnancy is limited. However, there were 24 women known to have taken clozapine during their pregnancy with no apparent adverse sequelae in their newborns (Michael Krassner, personal communication). Clearly, the number is too small to draw any conclusions regarding safety of use in pregnancy.

THERMOREGULATION

Most antipsychotic drugs are known to cause mild hypothermia in patients in addition to having the potential to produce a "drug fever." However, the frequency of this does not approach the rate at which hyperthermia occurs with clozapine treatment. This usually presents as a mild temperature elevation in the early stages of treatment that spontaneously subsides in a few days. In addition, clozapine-induced benign hyperthermia may be accompanied by an elevation in the white blood cell count. Clozapine-induced hyperthermia will often subside even with ongoing clozapine treatment. Occasionally, however, there are significantly large temperature elevations which persist and necessitate the interruption of treatment until the hyperthermia subsides. In these cases it is sometimes helpful to reintroduce clozapine at a slower rate of titration when the patient is afebrile. To our knowledge no patient has been unable to be retreated with clozapine because of persistent hyperthermia. It is important to emphasize that any patient who develops a fever while taking clozapine immediately requires careful medical workup including a complete blood count with

differential to rule out agranulocytosis. The differential diagnosis should also include: intercurrent infection, heat stroke, neuroleptic malignant syndrome, dehydration, and drug fever from concomitant medications.

DISCUSSION

The main point to be emphasized in the clinical management of patients receiving clozapine treatment is that its pharmacologic properties and the side effects which derive therefrom are numerous and very different from those of standard neuroleptic drugs. The physician's dictum "NIL PRIMUM NIL NOCERE" or "first, do no harm" is particularly apt for clozapine as the potential for iatrogenic morbidity is considerable. At the same time, the increased complexity and risk associated with clozapine treatment, are more than offset by the therapeutic advantages that it provides when properly used in appropriately selected patients. Many countries now have guidelines or formal procedures in place to ensure hematologic surveillance and enable early detection of agranulocytosis. Clinicians must rely on their own vigilance for the other potentially serious adverse effects of clozapine. However, with thorough knowledge of the drug's pharmacologic and clinical profiles, patients can be efficiently managed with a minimum of complications.

Clearly, the future will bring new atypical compounds with novel pharmacologic properties that will usefully contribute to our pharmacologic armamentarium. In this way clozapine will have served as a prototype which introduces clinicians to new approaches to the pharmacologic management of psychosis.

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