Clozapine: Evidence Based Medicine

8 years ago my life changed forever. Daniel, my kind wonderful and much beloved son, was entirely possessed by a terrible debilitating illness paranoid schizophrenia. At first my wife and I were overwhelmed and bewildered. We sought immediate care with his treating psychiatrist, but soon became disillusioned. Daniel was placed on 1 antipsychotic and progressed to a cocktail of antipsychotics that left him only a very stiff and hollow shell of his former humanity. We had every resource at our disposal and we were both possessed by the effort to make him better. We are both physicians and we had access to the best and the brightest, as well as the entire medical literature. Nevertheless, in the beginning we felt somewhat restrained in our efforts. Within 6 months and 4 failed antipsychotics we became entirely convinced that Clozapine was really the only option. We subsequently consulted a bevy of psychiatric experts, all of whom were unable or reluctant to prescribe this most feared "magic bullet." It took a full 18 months from the time of his diagnosis, his progressive social and cognitive decline, his persistent delusional belief that he was really a woman and my wife's and my own unremitting pressures to finally convince his "psychopharmacologist MD-PHD" psychiatrist to start clozapine.

Daniel has now been on clozapine since 3/8/6 and we have our son back. He has his associate degree in film and has been on the Dean's list for the last year. This Spring he is graduating from SUNY Purchase with a 4 year Bachelor's degree in screen writing and play writing. I will make no pretense; it was not always easy. We were told

in the beginning what an effective drug it could be, but we were also told time after time after time of the “extraordinary” difficulty many patients had tolerating its many side effects. We were warned that he could even die from its use. But clozapine is the “gold standard” of the antipsychotics for the treatment of refractory Schizophrenia and we could not agree more fully.

As it is, the initial response to any and all antipsychotics for initial treatment is reported to be anywhere from as low as 40% to as high as 70%. When a patient with Schizophrenia does not respond initially and requires a second antipsychotic, not including clozapine, the response rate is 8 to 12 % and usually this is only a partial response. However, when this same refractory patient is given clozapine the eventual response is 50 to 70%. A response to clozapine can be delayed for over 1 year so it is important not to give up prematurely. The present guidelines have clozapine as only a third line agent. There is now sufficient evidence to move clozapine up to a second line agent at the very least. My contention is that it should be the first agent used.

Is clozapine the best choice as a first line agent? Clozapine has shown advantages over other typical and atypical antipsychotics clinically, neuropsychologically, and socially. Clozapine contributes to the improvement of positive, negative, affective and cognitive symptoms in addition to reducing drug abuse, aggressive behavior by 38%, and suicide attempts by 70%. It is superior in terms of therapeutic adherence, quality of life, self-perceived satisfaction with treatment and overall survival. Furthermore clozapine is generic and despite the stringent monitoring required it has been demonstrated to be the most cost effective anti-psychotic. Recently special stress has been placed on the need for early intervention to stop clinical, neuropsychological.

Neurophysiological, and neurostructural decline. Effective treatment using pharmacology, psychotherapeutic modalities, and psychosocial support is critical as early in the illness as possible. A global supportive approach can change the trajectory of the illness and restore full function to the premorbid state. I believe that using clozapine first at the debut of the disease, gives the patient suffering from Schizophrenia the best chance for success. Increasingly I am not alone in this opinion as the groups in Spain, Finland and China have recently buttressed this position with hard data. Yet there remains so much fear of clozapine.

We were given dire warnings from multiple treating psychiatrists, and even our esteemed highly experienced psychopharmacologist. Given the clozapine gestalt of the mental health community I am not surprised that clozapine represents less than 4% of the antipsychotics prescribed in the US and less than 2% of patients are on this long term. Even in patients who have failed multiple antipsychotics and are classified as persistently psychotic where clozapine is the only rationale choice, the numbers go up to only 5.5% of all antipsychotics used. In the words of 3 of our psychiatric leaders Herbert Pardes MD, Jeffrey Lieberman MD, and Herbert Meltzer MD, the dramatic underutilization of clozapine remains psychiatry's single biggest failure to use evidence based medicine. In Meltzer's 2012 review, he conservatively estimated that over 40% of patients with Schizophrenia should be on long term clozapine.

It is a stark reality that most of treating providers live in fear of the liability and fear of the drug. But, let us look at the reality. Every year 5000 people with Schizophrenia in the US die from suicide. Herb Meltzer estimates that over 1500 of these deaths could have been prevented if the patients were on clozapine. Prescribers worry about

the risks of agranulocytosis. The fact is that over the first 5 years of the clozapine agranulocytosis registry 12 patients died from this. During this same interval the appropriate use of clozapine could have saved 8000 lives. We need to get past this irrational fear. The fact is every other antipsychotic has a worse litany of side effects without the potential for the consistent dramatic improvements often seen with clozapine. The evidence is irrefutable. Clozapine is the most effective antipsychotic. It is the only antipsychotic that significantly aides in both cigarette, and drugs of abuse cessation. It has been the one antipsychotic used that that most robustly allows patients to participate and succeed in social and cognitive rehabilitation programs. It is the antipsychotic that has the best acceptance from patients and the lowest discontinuation rate. Overall, it demonstrates an improved survival compared to patients on other antipsychotics or on no medicine. Most important it **gives the best chance for the sufferer to lead a full and meaningful life.** We have failed this so needy population so badly. At present it is estimated that only 14% of people with Schizophrenia have sustained recovery within the first 5 years following their first episode of psychosis.

We really have so much work to do.

Everyone talks about stigma, but the reality is stigma will continue to grow as long as there are paranoid schizophrenia patients heeding their tormenting inner command voices. In one recent study findings from the East London First Episode Psychosis study found a 38% prevalence of violence. Three highly prevalent delusions, persecution, being spied upon, and conspiracy led to anger resulting in serious violence in 12% of the sample population. Even we hid the knives early in my son's illness. We need to confront our own fears.

Most importantly we need to change the entire treatment paradigm. We need to treat with the best treatment as early as we can and the medical foundation of this treatment should be clozapine.

Clozapine is a difficult drug but if used properly, it can be life altering. Prior to initiation a complete physical including orthostatic blood pressures should be performed, and a complete set of labs including a cbc, chemistry panel, lipid profile, glycohgb, insulin levels, thyroid function, and anemia panel should be obtained. An EKG, cardiac echo, and a brain MRI and perhaps in selected patients an EEG should round out the initial evaluation. The complete blood work should be repeated no less frequently than every 3 months excluding the thyroids.

Clozapine by itself is the foundation, but to optimize recovery the patient with schizophrenia needs the medicine augmented and the predictable side effects ameliorated. Since a slow titration minimizes many of the side effects, in the severely psychotic patient another antipsychotic may need to be used initially. Clozapine in the severely agitated patient, where some sedation may be desirable, can be started on an AM and bedtime dosing schedule. The titration proposed in the package insert is very aggressive. I agree with starting at 12.5 mg, but only at bedtime. To minimize side effects, I would favor a titration schedule that only increases the daily dose by no more than 25-50 mg for any given dosing change and moving the total dose up no faster than 100 mg/daily during any 1 week time frame. Every week clozapine levels should be obtained and the medicine titrated to a minimal level of 350-420 ng/ml. As agitation wanes if the patient had required a second antipsychotic this should be cross tapered off as the dose of clozapine is titrated up. Every week when bloods are done for the

complete blood count the patient should have drug levels taken of all meds to assure compliance and especially in the case of clozapine adequate therapeutic dosing (bloods should be done to obtain trough levels if feasible). The patient should be seen every visit by the psychiatrist or psychiatric internist and the clozapine dosing should be slowly shifted by 50 mg at a time to bedtime if BID dosing was originally used, in order to decrease day time sedation and improve functioning.

Predictable side effects should be addressed at the start of therapy. In all not underweight patients and in those without a medical contraindication, metformin at 500 mg daily should be started in the morning. Every 2 weeks the dose should be titrated up by 500 mg to a dose of 1000 mg with breakfast and dinner. If nausea and or diarrhea are problematic the titration can be slowed. The rationale behind the use of metformin is that it improves glucose utilization and it minimizes weight gain, thereby helping the patient avoid obesity, the metabolic syndrome, and diabetes. Additionally metformin helps counteract the constipation caused by clozapine. As an aside, at least in rats, metformin has been demonstrated to increase neurogenesis. With metformin, all patients should be started on vitamin b12 1000 micro daily as metformin causes B12 malabsorption. For those who develop lipid abnormalities, consideration may be given to statin therapy and omega 3 fatty acids should be started. The addition of omega 3 fatty acids has been reported to help ameliorate some of the negative and positive symptoms of Schizophrenia.

Sinus tachycardia from the prominent anticholinergic effect of clozapine is an almost universal finding early in clozapine treatment. In fact, it is a handy surrogate marker for compliance. If the patient has no symptoms from the tachycardia and the heart rate is less than 120,

no treatment should be initially given. If the patient is symptomatic however, then a beta blocker should be prescribed. Inderal can safely be started at 10 mg twice a day and titrated upward weekly by doubling the dose until symptoms improve. Most patients will respond to fairly low dose treatment in the range of 40 mg twice a day. If the patient exhibits significant bronchospasm, metoprolol or another selective beta blocker can be substituted. Another benefit of beta blockers is that reducing the adrenergic tone often improves anxiety.

The need for further mood stabilization often remains an issue. Also, given the necessity of frequently requiring doses of clozapine over 600 mg and having to obtain therapeutic blood levels in the high 700-1000ng/ml range to achieve optimal therapeutic results, I strongly recommend adding either lamictal, gabapentin, or topiramate. Without anticonvulsants seizures can occur in 4.4% of patients taking clozapine at dosages above 600 mg as compared with only 2.7 % and 1.0% of patients receiving 300-600 mg/d and <300 mg/d, respectively. Although blood levels greater than 1000 are often seen, it is the rapid changes in levels that often present problems, rather than the level per se. So if the patient is clinically well, a “toxic” level is not truly toxic. Lamictal is often my first choice. Titration is well described and must be strictly followed to potentially avoid developing a rash. For the first 2 weeks start at 25 mg daily; in week 3 and 4, dose at 25 mg in the am and at bedtime. Subsequently, doses can be increased by 50 mg every 2 weeks. A usual therapeutic dose is 100 to 150 mg twice daily. Therapeutic drug monitoring should be employed. If the patient develops a rash from lamictal the drug must be stopped. There are a variety of studies showing lamictal augmentation in improving negative

symptoms and stabilizing mood in those treated with clozapine. Also, lamictal's actions through the NMDA receptor and glutamate pathway make it a theoretically appealing drug. Again, as it is titrated, levels must be followed with every change in dose and then monthly. Recently, a number of studies have documented gabapentin's utility in cigarette cessation, marijuana abuse, opiate addiction and alcoholism. This drug may be uniquely useful in the dually diagnosed and I have been using it more and more. I prefer to start with 300 mg and increase by 300 mg at bedtime to get to a therapeutic level. If daytime anxiety and agitation remain prominent a morning dose may be required. This is an excellent drug when anxiety remains a very prominent symptom. Finally, topiramate may be an excellent choice especially in those still having trouble with weight gain. This is an excellent anorectic drug and it is also is a good mood stabilizer. One potential downside of this drug is that it often causes some cognitive difficulties and excessive sedation. All three of these drugs can not only enhance the effect of clozapine but by prophylactically increasing the seizure threshold, allow clozapine to be used more safely at higher dosages.

One problem we ran into with Daniel, and which is very, very common, is excessive salivation and drooling. Despite clozapine being mostly anticholinergic it is also a potent M2(muscarinic-cholinergic) agonist. These receptors are prominently displayed in salivary glands, and when stimulated can lead to excessive salivation. This excess salivation has been associated not only with stigma-causing drooling, but also can lead to aspiration pneumonia. Early in treatment and with up titration this can be a difficult issue. Fortunately there is an easy remedy. We found that 2 puffs of sublingual 0.06% atrovent nasal

spray (anticholinergic agent) at bedtime dramatically decrease the excessive salivation. If daytime drooling is problematic, 2 puffs can also be used in the morning. Bed blocks to elevate the head of the mattress can also be used to decrease the risk of aspiration.

Constipation can be an intractable problem. Because of it's anticholinergic and sedative properties bowel transit time can dramatically slow. Clozapine can cause such severe obstipation that it can result in the bowels ceasing to work something called an ileus. Clozapine-induced ileus may be fatal. If a patient has a stool frequency of less than 4 to 5 times per week, intervention is necessary. Maintaining adequate hydration and exercise are important, but often are not enough. Bulking agents such as Metamucil should be avoided as this can further slow transit time. This actually could worsen the primary problem caused by clozapine. Cathartics and stool softeners are the way to go. Propylene glycol (miralax), and or lactulose routinely added to Colace and senna are reasonable choices. As needed milk of magnesia, and stimulant laxatives like dulcolax can be safely added. Linzess, linaclotide, is a new agent for constipation based irritable bowel disease. It works locally on the intestine to increase chloride and water secretion and has no systemic absorption. I have found it to be safe and quite an effective added therapy. However, because of its cost I reserve this only when other measures fail. Finally, acarbose, which causes carbohydrate malabsorption and helps with metabolic control, can be used, but many find the flatulence more than a bit annoying and embarrassing.

Now I would like to talk about hematologic side effects which remain the most feared complication. First Eosinophilia may indicate an allergic reaction and can be associated with myocarditis, pleural

effusions, hepatitis, and agranulocytosis. However, clozapine-induced eosinophilia without these other potentially life threatening side effects is a benign condition and should never lead to drug discontinuation. Eosinophilia (levels >3,000/microl) is usually transient and occurs commonly during the first year. Despite the conservative recommendation of the manufacturer John Kane states in a 2013 review: "It is our opinion that the potential consequences of discontinuation of clozapine outweigh this risk if all other medical conditions are excluded."

Neutropenia and ultimately agranulocytosis is the side effect most feared by clinicians and initially led to the withdrawal of clozapine from the market. The reality is much less daunting. The risk of agranulocytosis neutrophil count <500) is 0.7%, and the risk of neutropenia (500-1500) is 3%. With the current monitoring system fatal aganulocytosis occurs from 0-.03%. Neutropenia can occur any time during treatment but agranulocytosis occurs within the first 6 months over 95% of the time. If agranulocytosis does occur, this should lead to prompt clozapine cessation and there should be no re-challenge unless there is absolutely no alternative. With re-challenge, agranulocytosis recurs in approximately 50% of the patients. Neutropenia is an entirely different story. If neutropenia develops, monitoring should be increased to twice a week. Interestingly, a low initial neutrophil count is a risk factor for neutropenia but not agranulocytosis. Granulocyte colony-stimulating factor used every 14 days has been shown to be effective in resolving neutropenia. Lithium may also be used to improve the neutropenia. If lithium is used a dose sufficient to give a blood level of > 0.4 mmol/L is the goal. A simple remedy may be drawing the blood in the afternoon, as there is a

circadian rhythm of neutropenia with the lowest levels in the morning. Finally, since neutrophils that sit on the blood vessel wall are not measured and they can be demarginated from the blood vessel wall into the circulation with exercise, I routinely have my patients exercise in the gym prior to their blood draw.

Prescribers should be aware that discontinuing clozapine may have severe consequences, such as psychotic relapses and suicidal and homicidal behavior. Some side effects do not have a predictable course and may require a temporary cessation until parameters have stabilized; Examples of this include persistent neutropenia, neuroleptic malignant syndrome, and abnormal liver function. Other side effects are harmless and should not lead to discontinuation (e.g., benign hyperthermia, neutrophilia, eosinophilia, idiopathic sinus tachycardia, seizures). With agranulocytosis occurring in < 1% of cases , myocarditis in.015-0.188% , and severe cardiomyopathy in .02-.08% discontinuation is the only option, although re-challenge after stabilization (except with agranulocytosis) may be very carefully attempted.

Once the patient is successfully on clozapine and has therapeutic clozapine levels, I have had great success adding cognitive enhancers. Recently I have started patients on N-acetylcysteine at 1200mg twice a day. NAC add-on therapy has been shown to be a safe and often effective strategy for alleviating negative symptoms. The second drug I recommend starting is Namenda. A recent meta-analysis of it‘s use as an adjunctive therapy showed it was well tolerated and often improved negative symptoms. This medicine has a standard titration and in fact comes with a starter kit to get the patient up to 10 mg twice daily. This drug also works through the NMDA pathway. I suggest staying on this drug at full dose for at least 1 month and then carefully adding Aricept.

I would start very slowly at 2.5 mg in the morning and titrate up the drug every 2-4 weeks to a full dose of 10 mg. Aricept can show a dramatically beneficial effect on cognition in certain patients. Additionally it is a bit of an anorexic agent, often stimulates bowel activity, and slows the heart. So its side effects often improve those of clozapine. Finally if AM sedation is still problematic modafinil can be carefully and safely added in the AM. The precise mechanism of this wakefulness agent has not been fully elucidated, but there is a literature showing it-'s safety when used to combat clozapine-related sleepiness. The dosage should be started at 50 mg and can be titrated up to a maximum dose of 200 mg. Dose titration should be slow, no faster than 50 mg increase every month.

Two other issues with schizophrenia patients include concomitant mood disorders and Obsessive compulsive disorder. If either of these becomes an issue, Lexapro can be started at 10 mg and titrated to a maximum dose of 40 mg depending on clinical response. Any SSRI would do, but I find Lexapro effective and it does not appreciably interact with clozapine metabolism.

A critical caveat with clozapine use is an awareness of how it is metabolized in the P 450 A12 pathway. Cigarette cessation, depending on how much is smoked, can critically and quickly raise clozapine levels. As part of our global focus, as we strongly encourage cigarette cessation, we need to do this with a slow downward titration of nicotine. I have found the electronic cigarettes to be distinctly useful. As usage of cigarettes decreases, clozapine may need to be tapered down to avoid toxicity. Finally coffee consumption can dramatically

increase clozapine levels. Although coffee is useful to combat sedation, the patient should be discouraged from dramatically changing coffee consumption. Caffeine blocks the metabolism of clozapine via the P450 pathway and this effect can be quite dramatic, leading to a several fold increase in clozapine levels in some individuals.

So we have a medicine, which can if used properly, save countless lives. In expert hands clozapine can be the foundation on which to rebuild a life. We just need to devote the appropriate resources to this illness and take a holistic approach. My ultimate dream is establish a novel holistic-encompassing, dare I say embracing, Clozapine Clinic. My aspiration is that individuals with schizophrenia will not only get treated with clozapine but also they will be actively supported by a team of dedicated professionals. My ideal clinic will be staffed with a full-time psychiatric Internist and/-or a psychiatrist with a strong internal medicine training and will actively engage the patient in cognitive remediation, and cognitive behavioral therapy with a dialectic focus which emphasizes control of mood, appropriate social cueing, and social interactions. Family therapy will be heavily emphasized since an active supportive family can be the most important factor in recovery for not only the patient with schizophrenia but also for the family. There will be social workers assigned to assist with both educational and work opportunities. The best training for work is work. We believe that gainful employment should be the expectation. We will hire a peer support specialist to demonstrate to all of the patients and their friends and family what is possible. The peer specialist will be integrated into the clinic to provide a guide to a robust recovery. My hope is that the program will be integrated into both an undergraduate and graduate campus. Social isolation, one of the biggest curses of

those suffering from schizophrenia will be obviated by a club-house setting based on the Fountain House model. Here they will socialize and work. Active physical training with a focus on aerobic, I hope running, and weight training will be a major part of the program. From this I hope to recruit future runners for our charity, “Team Daniel Running For Recovery From Mental Illness.” Nutrition education from cooking right to counting calories will be another focus. The average life span of someone suffering from schizophrenia is 25 years shorter than the general population. 30-40% of this decrease in life expectancy is from suicide, but another large portion, 40-50%, of this premature mortality comes from remediable behaviors, such as poor nutrition, lack of exercise, illicit drug abuse, alcohol, and cigarette smoking. Cigarettes alone decrease the average life span by 14 years. Drug counseling, alcohol abstention, and cigarette cessation will be exhaustively included. Most importantly we will show that expertly managing clozapine makes a huge difference. In time we will show that this approach will restore this most downtrodden population to a fulfilling life. Lastly we will always strive for more and better therapy. We will combine advanced imaging studies to follow the patients longitudinally. We will see where the brain is broken and in time develop new medicines and strategies. We will give the best treatment now and continue to develop better treatments in the future. My hope is that this dream becomes the new model to treat schizophrenia. We need to move forward, as the need is large, and we know the consequences of inaction.This is only a start, but just imagine what we can achieve. Let the nightmare stop and the dream begin. Give everyone the same opportunity that my son Daniel has had.

This is all just a start but we have the capacity to make such a difference. The system needs to be fixed and our patients need to stop suffering, and regain their sense of identity and purpose. We can do this, we must do this—we just need the will.