**CLOZAPINE: THE TEAM DANIEL PROTOCOL – A basic outline August 23,2021**

*Rachel Streiff, our Research and Data Analyst, with the approval of Dr. Rob Laitman and Dr. Ann Mandel Laitman, has written the following basic outline of Clozapine use and the TEAM DANIEL protocol.*

**A.  Clozapine Dosing schedule:**

12.5mg daily the first week. Increase by 25mg PER WEEK (not per DAY). In very agitated or acute patients 50mg increase over a week, in rarer cases 75mg.

This approach is VASTLY slower than the drug manufacturers’ recommendations and how most physicians have been trained.  Traditional methods with faster clozapine introductions (as high as 150mg to 200mg per week increases) frequently cause serious side effects in patients (myocarditis, intestinal blockage, seizures, severe orthostasis etc.).  This approach can tragically sabotage a patient’s experience with clozapine and reduce their chances of achieving meaningful recovery.  This especially happens with less experienced providers, and during hospitalizations due to their desire to turn patients over quickly.

**B. New or worsening symptoms in the first few days/weeks/months of clozapine:**
Clozapine works differently than other antipsychotics- it takes months, sometimes years, to be fully effective.  Clozapine’s mechanism of action involves healing a damaged brain, as opposed to just blocking dopamine like other medications do.  Clozapine is the LONG GAME.  ***A marathon, not a sprint.*** For this reason another fast-acting antipsychotic (I.e Zyprexa) is usually required during the initial weeks and months of clozapine initiation.  Other antipsychotics should be slowly tapered down and discontinued while Clozapine is tapered up. Not all physicians have training and experience with the long cross-tapers required to transition to clozapine.  New or worsening symptoms could be either breakthrough psychosis or withdrawal symptoms tied to discontinuing the previous antipsychotic too quickly.  And even with the best of doctors this period is CHALLENGING.  Usually, by definition, if we are at the point of introducing clozapine we are already dealing with treatment-resistant symptoms.  Plainly put: psychosis sucks.  There’s no magic pill.  All we know is that over the long term clozapine is the best and safest antipsychotic IF ADMINISTERED PROPERLY.

**C. Side effects of clozapine:**
Clozapine is not a single-drug solution- it cannot be given alone as there are numerous side effects that must be treated.  However, in 85% of TEAM DANIEL patients clozapine is the ONLY antipsychotic.  “Mixing” antipsychotics rarely helps psychosis compared to using clozapine as the sole antipsychotic.  Usually mixing just adds to side effects.

Clozapine significantly lowers seizure threshold, profoundly alters metabolism, dramatically slows bowel activity, greatly increases saliva production, and is highly sedating.  These five side effects are universal.  Nearly ALL of Team Daniel patients are on:

-an anti-seizure medication (lamotrigine is the favorite) to prevent seizures.

-stool softeners and laxatives (colace and dulcolax) to prevent constipation

-metformin to prevent weight gain and diabetes

-sublingual atropine drops or ipratroprium spray to control over-salivation, usually at bedtime.

Sedation is difficult to treat.  Clozapine patients need about 12 hours of sleep a night.  Over time this may come down, but many clozapine families reach a point where the benefits to their loved one’s brain, function, life and livelihood are absolutely worth their need for more sleep than the average person.  Strategically splitting doses, morning exercise, moderate coffee, anti-narcolepsy medications like Provigil or Nuvigil can help prevent daytime drowsiness so that the patient is more alert during waking hours.  But, so far there is really no way around the clozapine extended sleeping hours.  This is the clozapine lifestyle- the best we can do is embrace it.  Most of us feel this is a small price to pay for our loved one’s wellbeing.

Also: the TEAM DANIEL approach NEVER uses stimulants (Adderall, Ritalin, etc) as these will significantly worsen or trigger psychosis.

Some other side effects that are common and treatable with adjunctive meds: frequent urination, rapid heart beat, orthostasis/dizziness, nausea/vomiting.

**D. Confusion about blood tests…**

There are TWO kinds of blood tests you see us discuss frequently:

1. The mandatory weekly, bi-weekly, or monthly counts of ANC and WBC required for the clozapine REMS (Risk Evaluation and Mitigation Strategies).  This ensures patients are not developing the rare serious side effect of agranulocytosis (low white blood cell count).  Without a current wbc count entered into the REMS system your doctor can’t prescribe clozapine and your pharmacy can’t dispense it.

2. Therapeutic Drug Monitoring (TDM).  This is a non-mandatory, extra test, that measures serum concentrations of clozapine and the norclozapine metabolite in the blood, in units of ng/mL.  Your doctor requests this extra test to see how a patient is metabolizing the drug and help determine the appropriate clozapine dose.  It is best to run this test frequently while initiating clozapine, when making dosage changes, and when confirming medication compliance.  The blood draw MUST be done 12 hours after the evening dose and before the morning dose in order to be considered accurate.  This is why it is sometimes called a “12 hour trough level.”

TDM is very important to help determine the appropriate dose for each patient.  Do NOT assume your doctor is routinely measuring these levels- you may need to request these extra tests.  If your doctor says “the blood work is fine” they are referring to item #1 which is essentially pass/fail criteria.  For item #2 the results will be numerical values that look like this example:

Clozapine: 622 ng/mL
Norclozapine: 327 ng/mL
Total: 949 ng/mL
Cloz/Norclozapine Ratio: 1.9

Note that some labs (especially in labs outside of the USA) report higher values in different units of nmol/L - you can roughly divide these by 3 to get the values converted to ng/mL.

Historically, a clozapine level between 350 ng/mL and 650 ng/mL was considered therapeutic, with 1000 ng/mL considered the upper limit.  However, about HALF of Team Daniel patients with schizophrenia spectrum disorders have clozapine levels over 730 ng/mL and a fourth are over 900 ng/mL, with a max of 1500 ng/mL.  Achieving these higher levels is ALWAYS done slowly, by a skilled physician, and done in conjunction with other medications like like lamotrigine to prevent side effects (specifically seizures).

In general terms, clozapine is good (antipsychotic benefits) but norclozapine is bad- responsible for side effects.  Thus, the higher the ratio the better.

Skilled doctors may try to increase the clozapine levels, lower norclozapine levels, and increase the ratio by augmenting clozapine with fluvoxamine (Luvox).  This must be done very slowly with a “microdosing” approach starting with 6.25mg of Luvox - a quarter of the smallest available pill.  Also, this must only be done with proper seizure prevention in place (like Lamotrigine).  This approach can also be used to lower the clozapine dose but still achieve the same benefits.

Smoking SIGNIFICANTLY reduces both clozapine and the clozapine/norclozapine ratio, and we highly advise SLOWLY switching to vaping or other forms of nicotine.  Abruptly stopping smoking can spike clozapine levels and cause seizures.  Dr. Laitman frequently uses Chantix for this effort, which is usually well tolerated in people with psychotic spectrum disorders.

**D.  What is an optimal clozapine dose?**

TEAM DANIEL has patients between 6.25 mg per day and 900 mg per day.  This wide variation is because there is extreme diversity in the way individuals metabolize and respond to clozapine.  The only way to find the optimal dose in each unique individual is to start low, using very slow increases, with close and careful monitoring of the patient and using TDM measurements as a guide.

For reference, on TEAM DANIEL the median daily dose is 300mg per day for schizophrenia spectrum and 100mg per day for bipolar disorders.  Drug-induced psychosis, depression with psychosis and personality disorders are usually treated with less than 100mg per day.  But there is a VERY wide range of doses because each person is so unique.  Also keep in mind many of these Team Daniel patients (about 60%) have been augmented with fluvoxamine.

These are some of the most frequent discussions in this forum.  The BEST THING YOU CAN DO is get a copy of Dr. Laitman’s book: **MEANINGFUL RECOVERY from Schizophrenia and Serious Mental Illness with Clozapine** as he clarifies ALL of these items and MUCH more.  **The Clozapine Handbook** (Meyer/Stahl) is also very useful.  We highly advise getting additional copies for your doctor.  If you cannot afford a book, occasionally TEAM DANIEL has generous donors willing to help. Contact an admin and we will add you to a waiting list for a book.

*Posted August 16 on FaceBook : TEAM DANIEL and the Clozapine Community*