New Requirements for Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program to Begin February 28, 2019

- Clozapine is associated with severe neutropenia, defined as an absolute neutrophil count (ANC) below 500 cells/microliter.
- The Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program is required by the Food and Drug Administration (FDA) for clozapine to ensure that the benefits of the drug outweigh the risks of severe neutropenia.

Effective February 28, 2019, the Clozapine REMS Program has new requirements for all clozapine prescribers and pharmacies that dispense clozapine.

Highlights of the modified Clozapine REMS Program requirements are as follows:

Outpatient clozapine prescribers:

- Prescribers must certify in the Clozapine REMS program.
- Ensure that all patients receiving clozapine are enrolled in Clozapine REMS prior to clozapine being dispensed. If patients are not enrolled in the Clozapine REMS program, clozapine will not be dispensed.
- Obtain and submit an ANC in accordance with clozapine prescribing guidelines; a current ANC must be documented in the REMS Program database prior to clozapine dispensing. If a current ANC is not on file, clozapine will not be dispensed.
- If the last ANC indicates moderate or severe neutropenia, clozapine will not be dispensed unless the prescriber documents that benefits outweigh the risks of neutropenia.

Inpatient clozapine prescribers:

- Inpatient clozapine prescribers are not required to be certified if prescribing clozapine to patients already enrolled in the Clozapine REMS program.
- If clozapine is started on the inpatient unit, providers must enroll patients in Clozapine REMS Program *prior* the patient receiving their first dose of clozapine.

Pharmacies that dispense clozapine:

- Pharmacies must be certified in the Clozapine REMS Program prior to dispensing clozapine.
- Outpatient pharmacies must obtain a “Pre-Dispense Authorization” (PDA) prior to dispensing clozapine. Outpatient pharmacies will not receive a PDA if an ANC is not on file, or if a patient has an ANC that indicates moderate or severe neutropenia without a prescriber treatment rationale on file.
- Inpatient pharmacies are required to complete an “Eligibility Check” prior to dispensing clozapine. If the patient is not enrolled in the Clozapine REMS Program, a PDA will not be issued and the Eligibility Check will be unsuccessful.
- Pharmacies will no longer be able to enroll patients in the Clozapine REMS Program. Patients must be enrolled by prescribers or the prescriber designee.
- Pharmacies are encouraged to submit ANCs to the Clozapine REMS program when a pharmacist is aware of a more current ANC.

For more information, visit https://www.clozapinerems.com/CpmgClozapineUI/home.u.

Critical Decision Points for Augmenting Interpersonal Psychotherapy for Depressed Adolescents

- A new randomized trial published in the Journal of the American Academy of Child and Adolescent Psychiatry by Gunlicks-Stoessel, et al. (2019) provides empirical evidence that increasing the frequency of interpersonal psychotherapy (IPT) early in treatment can be beneficial for depressed adolescents who do not respond to weekly therapy.
- 40 adolescents ages 12-17 with depression began treatment with 12 sessions of IPT delivered over 16 weeks.
- Adolescents were randomized to be evaluated for response to therapy at either week 4 or week 8 of treatment. Non-response to therapy was assessed by scores on the Hamilton Rating Scale for Depression (HAM-D).
- Non-response to IPT-A treatment was defined as less than 20% reduction in baseline symptoms as measured by the HAM-D in adolescents evaluated at week 4, or less than 40% reduction in the HAM-D score for those evaluated at week 8.
- Adolescents with adequate response at either week 4 or week 8 were assigned to continue weekly IPT-A sessions. Adolescents with inadequate response were randomly assigned to either more frequent (twice weekly) sessions of IPT-A or addition of fluoxetine to the once weekly IPT sessions.
- Outcomes were measured using the Clinical global Assessment Scale, Social Adjustment Scale—Self Report, and Columbia Suicide Severity Rating Scale.
- The study found no significant differences in outcomes when IPT was augmented with fluoxetine at week 4 versus week 8 in adolescent non-responders. However, adolescent non-responders who were identified after 4 weeks of weekly IPT and had treatment augmented with twice weekly IPT sessions had more favorable outcomes as measured by the three rating scales compared to those who were evaluated after 8 weeks of therapy and received fluoxetine augmentation.
- The study authors concluded that despite the small sample size and limitations of the current study, therapists should routinely monitor symptoms over the course of IPT treatment. Therapists should consider augmenting treatment for insufficient responders by increasing the frequency of sessions to twice per week over a period of 4 weeks, as long as it is initiated early in treatment. Early intervention with more intensive therapy sessions has promise to significantly improve depressive symptoms in adolescents.

Reference:

Gunlicks-Stoessel, M, Mufson L, Bernstein G, Westervelt A, Reigstad K, Klimes-Dougan B, et al. Critical decision points for augmenting interpersonal psychotherapy for depressed adolescents: a pilot sequential multiple assignment randomized trial. JAACAP. 2019; 58(1): 80-91.

Association of Prenatal Exposure to Valproate and Other Antiepileptic Drugs with Risk for Attention Deficit/Hyperactivity Disorder in Offspring

- A Danish study by Christensen, et al. (2019) in *JAMA Network Open* explored the risk of attention deficit/hyperactivity disorder in children prenatally exposed to valproate versus other anti-epileptic drugs (specifically carbamazepine, oxcarbazepine, lamotrigine, or clonazepam) versus no pre-natal exposure to anti-epileptic drugs
- The population-based cohort included 913,302 children, of which 580 children were identified as having prenatal valproate exposure.
- Compared with mothers who did not use valproate during pregnancy, mothers who did use valproate during pregnancy were younger, more often diagnosed with epilepsy and psychiatric disorders, and were more often smokers.
- The study found that children with prenatal exposure to valproate had a 48% increased risk of attention deficit/hyperactivity disorder compared to children without prenatal valproate exposure.
- The association between prenatal exposure to valproate and increased risk of ADHD persisted after adjusting for maternal psychiatric disorders, maternal epilepsy, maternal diabetes, maternal age, sex, year, of birth, and number of children. The association between prenatal exposure to valproate and increased risk of ADHD also remained after excluding mothers who smoked during pregnancy.
- According to the study, no statistically significant associations were found between exposure to the other antiepileptic drugs studied and attention deficit/hyperactivity disorder.
- Some limitations of this study include that women who remain on valproate therapy during pregnancy may differ in terms of the severity of symptoms compared to those not on valproate treatment and inability to quantify the exact amount of valproate taken since the study was based on data from a national registry. Additionally, the study did not control for medications other than antiepileptic drugs that the mother may have taken during pregnancy.

To read the full study, visit doi:10.1001/jamanetworkopen.2018.6606.

Reference:

Christensen J, Pedersen LH, Sun Y, Dreier W, Brikell I, and Dalsgaard S. Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention-deficit/hyperactivity disorder in offspring.JAMA Netw Open. 2019; 2(1): e186606. Available at: doi: 10.1001/jamanetworkopen.2018.6606.