What reactions can a patient experience upon discontinuation of clozapine, in other words, is there a withdrawal syndrome? Is dramatic weight loss seen as one of these symptoms?

Background:
Clozapine is an atypical antipsychotic that differs from typical and other atypical antipsychotics as well. It differs from typical antipsychotics due to its low incidence of extrapyramidal symptoms and slight effect on dopamine sensitive prolactin. Another factor that makes it unique from most antipsychotic medications is its indication for treatment-refractory schizophrenia. This medication also has distinguishing features in its pharmacology due to its weak association with D2 receptors compared to the other atypicals. Clozapine primarily blocks D1 and D4 receptors. Furthermore, it has stronger anticholinergic properties versus other atypicals. However, despite its advantages, the use of clozapine can result in serious adverse effects such as orthostatic hypotension, sialorrhea, seizure, hepatotoxicity, and agranulocytosis. Because of the possibility of agranulocytosis, clozapine requires routine monitoring of WBC and ANC.

Due to these adverse events and the need for close monitoring, clozapine often leads to issues with compliance. There have been a number of case reports that have shown that abrupt discontinuation of clozapine is correlated with relapse or withdrawal effects. Often these symptoms become present within 2-3 days of termination with clozapine and include anxiety, insomnia, motor restlessness, psychotic symptoms, tardive dyskinesia,
confusion, nausea, and altered consciousness. There are a couple of theories on the cause of this withdrawal syndrome of clozapine. One theory describes the marked decompensation to be due to D2 supersensitivity, but this seems improbable because it has very limited effects on D2 receptors. The second theory suggests that the withdrawal from clozapine occurs as a result of cholinergic rebound and gamma-aminobutyric acid (GABA) supersensitivity. Verghese, et al believe that it is strongly anticholinergic because of the similar response to sudden withdrawal of tricyclic antidepressants which also exhibit intense anticholinergic effects. One study demonstrated that withdrawal of tricyclic antidepressants was comparable to the administration of cholinomimetics. Within hours to 2-3 days, symptoms such as flulike syndrome, nausea, vomiting, anxiety, irritability, insomnia and Parkinsonism were reported. Therefore, it was observed that not only the symptoms, but the time course was similar between clozapine withdrawal and the administration of cholinomimetics. The worsening of tardive dyskinesia that is seen in some patients after discontinuation of clozapine is thought to be a result of its effects on GABA. GABA turnover has been reported to increase in the substantia nigra with clozapine. By stopping clozapine, development of GABA supersensitivity can occur within 1 week, and usually returns to normal after 2 weeks, which may explain why tardive dyskinesia appears soon after clozapine’s discontinuation.

Another concern that has been discussed involves switching to different antipsychotics. This may indicate why clozapine withdrawal occurs when changing to another antipsychotic such as risperidone. These two medications have very different receptor profiles, and therefore may not be comparable in efficacy. Risperidone has a much stronger affinity for D2 and serotonin2A compared to clozapine which has minimal effects on D2 and moderate effects on serotonin2A. It is due to the many uncertainties of the causes of decompensation following discontinuation of clozapine that has led to the current interest in the clinical significance of clozapine discontinuation and if there is a withdrawal syndrome.

Literature Review:
Tollefson et al conducted a controlled double-blind study in 106 patients to determine if olanzapine could be substituted for clozapine with minimal adverse events with discontinuation symptoms blocked and efficacy maintained or improved during treatment with olanzapine. The patients enrolled in the study were required to have met DSM-IV diagnostic criteria for schizophrenia, and received clozapine treatment for at least 4 weeks prior to the study. During study period I, there was a 2-12 day screening period where clozapine was tapered at a rate of 50mg/day maximally to a dose of 300mg per day. Study period II followed, and randomized patients to receive olanzapine 10mg per day or placebo for 3-5 days. Patients were observed for any signs of relapse or discontinuation related psychosis. These signs included worsening of at least one of the following: schizophrenic reaction, hallucinations, delusions, or abnormal thinking. For 1 week (study period III), all the patients were administered olanzapine 10-20mg per day. Study period IV lasted 8 weeks and involved the titration of olanzapine to 10-25mg per day. Any patients who were not stabilized by day 5 of the study discontinued treatment. Standard history, physical examination and a laboratory profile were performed on the patients at the initial visit. At the initial visit, after study period II, and weekly throughout study periods III and IV, clinical assessment were determined using the CGI Severity of Illness scale, Positive and Negative Syndrome Scale (PANSS), BPRS, Mini-Mental Status Exam, as well as others. The results of the study demonstrated that during study period II 24.5% of the patients randomized to receive placebo experienced discontinuation-relapse psychosis which was evident within an average of 2.8 days from the discontinuation of clozapine. As for the patients receiving olanzapine, psychotic discontinuation symptoms were significantly lower (p= 0.017). The placebo treatment group also showed worsening in PANSS total change score compared to the olanzapine treatment group (p= 0.036), whereas olanzapine treated patients showed some improvement. By study period III and IV, adverse events related to treatment were higher and more persistent in those patients who initially received placebo (p= 0.032). Yet the symptoms related to clozapine withdrawal (hallucinations and paranoid reaction) did not have significant differences between the 2 treatment groups. The authors concluded that at an appropriate dose of olanzapine, careful observation and overlap, olanzapine can be substituted for clozapine safely.
Yovtcheva et al described 2 cases concerning the reemergence of tardive dyskinesia after discontinuation of clozapine treatment. The first case discussed a 52 year old white male diagnosed with chronic undifferentiated schizophrenia at age 20. His past medication history for this illness included oral haloperidol 60mg per day, haloperidol decanoate 150mg/28 days along with oral haloperidol 40mg per day, fluphenazine decanoate 37.5mg/2 weeks and thioridazine 600mg per day. This patient was receiving typical antipsychotic medications for approximately 15 years. In 1990, the patient began to show symptoms of tardive dyskinesia and worsened over the next 3 years. His symptoms included choreoathetotic movements of the face and hands. Eventually, clozapine was initiated to attempt to resolve or improve his tardive dyskinesia. Clozapine was titrated up to 600mg per day over a 5 week time period. The patient’s tardive dyskinesia, psychogenic polydipsia, and psychotic symptoms improved significantly after 3 months of treatment with clozapine. Decreases in his AIMS and BPRS scores were observed. His clozapine treatment was continued for the next 2.5 years until the patient developed a fever of unknown origin with pancytopenia. Major symptoms of tardive dyskinesia appeared within 24 hours of discontinuing treatment with clozapine, and over the next week he had recurrences of his psychotic symptoms including paranoid delusions, looseness of associations and auditory hallucinations. Initiation and titration of risperidone to 6mg per day, improved his psychotic symptoms but did diminish the symptoms of tardive dyskinesia. The second patient was a 68 year old white male diagnosed with chronic undifferentiated schizophrenia. His past medication history included oral haloperidol 30mg per day, haloperidol decanoate 150mg/28 days along with oral haloperidol 20mg per day, thioridazine 600mg per day, and pimozide 4 mg per day. After 20 years of treatment with these typical antipsychotics, the patient showed symptoms of tardive dyskinesia in 1993. His psychotic and tardive dyskinesia symptoms worsened even more by 1996 and resulted in dyskinetic movements involving the face, trunk, and extremities. Initiation and titration of clozapine to 125mg per day over a few weeks resulted in significant improvement in AIMS and BPRS scores. After 3 months, the patient demonstrated muscle weakness, hypercalcemia, and hyperphosphatemia due to multiple myeloma. Therefore, clozapine was discontinued and within 48 hours the patient had severe tardive dyskinesia and recurrence of paranoid delusions and bizarre behavior. Olanzapine was started at 10mg per day with no effect on tardive dyskinesia or his psychotic symptoms.

Radford et al reported a case of a 21 year old white male diagnosed with schizophrenia. Initially, the patient was receiving sertraline for his negative symptoms. When clozapine was initiated and titrated to 200mg, sertraline was gradually decreased from 200mg to 50mg daily. The patient showed good improvement with clozapine over 9 months, but the patient disliked the frequent blood draws so it was discontinued after stopping sertraline treatment. Due to the low dose of clozapine, the medication was discontinued abruptly rather that gradually decreased. The following day, risperidone was initiated at 1mg at bedtime and increased to 2 mg the next day. After the first 2mg dose, the patient had a dystonic reaction that was treated with diphenhydramine 50mg IM, then 50mg by mouth for 4 more doses at home. Even after discontinuation of risperidone and initiation of benztropine 1mg by mouth every 6 hours, the patient continued to experience dystonia. On day 3, nausea and vomiting began to occur, he was admitted to the emergency room for hydration and antiemetic treatment until resolution of dystonia within the next 36 hours. The authors concluded that risperidone and an anticholinergic agent should be combined to avoid the cholinergic rebound due to clozapine, slowly taper clozapine, or overlap treatment with clozapine and risperidone for a small period of time and then taper the clozapine.

Malhotra et al reported a case concerning a 26 year old white male diagnosed with schizoaffective disorder at the age of 8, and was not achieving successful treatment until initiation of clozapine. After 9 years of treatment with clozapine, the patient began complaining of chest pain with dyspnea on exertion. He was hospitalized twice over the following 4 months and was diagnosed with pericarditis, polyserositis, and leucopenia. His medications at the time included clozapine 550mg per day, sertraline 250mg per day, divalproex sodium 1000mg per day, and benztropine 4mg per day. After a variety of tests, Epstein-Barr, Coxsackie, HIV, infections, vasculitis, tuberculosis, malignancy and connective tissue diseases were all found to be negative. After discontinuation of clozapine, olanzapine was started at 10mg per day within 48 hours. The benztropine 4mg per day and sertraline 250mg per day were continued, and the divalproex sodium was discontinued. Upon
resolution of pain, dyspnea, and psychotic symptoms, the patient was discharged. However, 4 days later, the patient began complaining of intractable nausea, vomiting, insomnia and restlessness. No paranoid ideations, hallucinations or delusions were reported. On day 2 of admission, psychotic symptoms began to increase and received haloperidol 2mg and benztropine 4mg intravenously. Additions were made to his regimen including lozapine 10mg IM in the morning and 25mg IM in the evening, and cyproheptadine 2mg three times a day on the third day of admission. This new regimen significantly improved the cholinergic rebound and decreased the symptoms of psychosis. By the sixth day, the patient was well enough to be discharged from the hospital. After 4 weeks of remaining stable, the patient wished to restart clozapine to improve his condition, and remained stable on it for 2 years. The authors concluded that there is not enough information about abrupt withdrawal of clozapine and the clinical deterioration that may be associated with it.  

Tanriverdi and Yazici reported a case involving a 30 year old woman diagnosed with chronic paranoid schizophrenia since 1987. Her past medication history included haloperidol, chlorpromazine, and trifluoperazine, all of which resulted in partial response. During a hospitalization in 1994, she was started on clozapine due to the inadequate response to the other antipsychotic medications and severe extrapyramidal side effects (muscle rigidity, tremor, difficulty swallowing, and akathisia). Clozapine was initiated at 12.5mg twice daily and titrated to 400mg per day over 2 weeks. By the 8th week of treatment, her condition had improved significantly demonstrated by her reduction in scores of BPRS, SANS, and SAPS. However, due to increases in her leukocyte (3000/mm$^3$) and granulocyte (1800/mm$^3$) counts, clozapine was discontinued. It was replaced by thioridazine 400mg/day. The patient reported sleeping only a few hours that night and sweated profusely. The following day, her psychotic symptoms increased (i.e. called fire department because the city was burning) and was afraid of being harmed by other people. Then the patient believed that a close relative ordered her to jump off the fourth floor of a building and was brought to the emergency room by her parents for paraplegia. Her total leukocyte count and granulocyte count upon admission were 2400/mm$^3$ and 1200/mm$^3$, respectively. The authors concluded that abrupt discontinuation of clozapine should be closely monitored due to the risk of a sudden recurrence of psychotic symptoms.

Summary:
Based on the case reports and study reviewed, more studies need to be conducted to determine the cause of relapse in schizophrenia after discontinuation of clozapine. With the lack of information available to clinicians, it is difficult to approach stopping clozapine and initiating another antipsychotic. However, it seems likely that upon discontinuing clozapine there is an anticholinergic rebound that results in increased psychotic symptoms including delusions, hallucinations, and abnormal thinking. Symptoms of nausea, anxiety, insomnia, confusion and tardive dyskinesia can also occur. However, with the case reports and study reviewed, no reports were made concerning weight loss as an occurrence with clozapine termination.

Most recommend that clozapine should be tapered down slowly, with a slight overlap of the new antipsychotic, and gradually increase the new neuroleptic. Another concern is which antipsychotic to choose as a replacement for clozapine. This may be best determined by looking at the receptor profiles of each medication. Olanzapine appears to have a similar profile to clozapine including affinity for D$_{1-4}$, 5-HT$_{2A-2C,3,6}$, muscarinic1-5, and cholinergic. It also showed significant differences compared to the placebo in the study conducted by Tollefson et al. Olanzapine decreased the incidence of psychotic symptoms significantly compared to placebo after tapering of clozapine. As for risperidone, the case report discussed showed a patient who experienced a dystonic reaction after abrupt discontinuation of clozapine and initiation of risperidone. Also, it was noted by Vergheze that a number of clinicians observed significant decompensation in patients started on risperidone. This may also show that the receptor profiles of antipsychotics need to be somewhat similar in order to switch between the medications without a recurrence of psychotic symptoms. However, some of the case reports showed that initiation of olanzapine did not help in reducing the withdrawal syndrome (Malhotra et al and Yovcheva et al).
In conclusion, there is little research concerning the discontinuation of clozapine, comprising of a number of case reports describing the relapse of symptoms. However, there is reason to further study this subject involving more randomized, double-blind studies such as the olanzapine trial conducted by Tollefson. For now, it should be recommended to taper the clozapine dose slowly, allow some overlap between clozapine the antipsychotic being initiated, and gradually increase the dose of the new antipsychotic. When adjusting these medications, the patient should be closely monitored for signs of relapse or withdrawal including symptoms of increased psychosis, anxiety, nausea, insomnia, and extrapyramidal symptoms.

References: