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# Psychiatric drug-induced Chronic Brain Impairment (CBI): Implications for long-term treatment with psychiatric medication[1]

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**Abstract.** Understanding the hazards associated with long-term exposure to psychiatric drugs is very important but rarely emphasized in the scientific literature and clinical practice. Drawing on the scientific literature and clinical experience, the author describes the syndrome of Chronic Brain Impairment (CBI) which can be caused by any trauma to the brain including Traumatic Brain Injury (TBI), electroconvulsive therapy (ECT), and long-term exposure to psychiatric medications. Knowledge of the syndrome should enable clinicians to more easily identify long-term adverse effects caused by psychiatric drugs while enabling researchers to approach the problem with a more comprehensive understanding of the common elements of brain injury as they are manifested after long-term exposure to psychiatric medications. Treatment options are also discussed.

Keywords: Psychiatric drugs, adverse effects of psychiatric drugs, cognitive dysfunction, dementia, chronic brain impairment (CBI)

## 1. Introduction

Every type of psychiatric medication initially produces effects that are specific to the particular drug's unique impact on neurotransmitters and other aspects of brain function. For example, the SSRI antidepressants block the removal of the neurotransmitter serotonin from the synapses; the antipsychotic drugs suppress and block dopamine neurotransmission; and the benzodiazepines amplify GABA neurotransmission which in turns suppresses overall brain function.

Although all psychiatric drugs have specific initial biochemical effects, over time other neurotransmitter systems react to the initial effects and broader changes begin to take place in the brain and in mental functioning.

## 2. Antipsychotic-induced brain damage and dysfunction from long-term exposure

As an example, the neurotoxicity of antipsychotic drugs has been studied and demonstrated for decades. Antipsychotic drugs produce Neuroleptic Malignant Syndrome with nearly identical brain pathology to that of a viral encephalitis (encephalitis lethargica or von Economo's disease), which was epidemic

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around World War I [1]. Clinical doses of haloperidol and olanzapine over 17–27 months duration in macaque monkeys have been shown to cause 8%–11% shrinkage in tissue weight (indicating cell death) throughout the brain [2]. The toxicity of the antipsychotic drugs on a cellular level includes the inhibition of most enzyme systems in mitochondria [3–5]. Kim et al. [5] observed that chronic blockage of dopamine neurotransmission by antipsychotic drugs "results in persistently enhanced release of glutamate, which kills striatal neurons".

Dwyer et al. reviewed the "cytotoxic properties" of the older antipsychotics, which they describe as "well known" [6]. Their own studies of the atypical antipsychotic drugs found them cytotoxic as well, but less so than the older drugs. In defense of olanzapine, the researchers stated that olanzapine "actually stimulated proliferation of neuronal cells," implying this is potentially beneficial. However, neurons very rarely proliferate and are only known to do so in response to injury. Second, many studies of drug-induced neuronal growth have found that the cells look grossly abnormal under the microscope [7].

Tardive dyskinesia, a potentially severe and usually irreversible movement disorder associated with antipsychotic treatment, is caused by damage to the basal ganglia where dopaminergic neurons are clustered. In response to the antipsychotic-induced blockade of dopamine neurons, the dopamine receptors grow in sensitivity and proliferate in number. This eventually leads to the production of abnormal movements. However, the basal ganglia are also involved in mental function, and tardive dyskinesia, as well as most or all other diseases of the basal ganglia (e.g. Huntington's chorea), eventually lead to dementia. All neuropsychiatric studies of patients with tardive dyskinesia have revealed an associated impairment of cognitive and affective functioning [7–9].

A persistent withdrawal tardive psychosis has been identified, confirming long-term chronic changes in mental function [10]. Many patients develop Neuroleptic-Induced Deficit Syndrome (NIDS) with cognitive and affective losses [11]. One of the few studies to address the neuropsychiatric condition of a large group of individuals exposed to antipsychotic drugs found generalized cognitive dysfunction [12]. Two recent studies have shown atrophy of the brain attributable to the antipsychotic drugs in long-term treatment of patients diagnosed as schizophrenic [13, 14].

Studies of all classes of psychiatric drugs have yielded similar findings of mental dysfunction and atrophy of the brain in humans after long term exposure, as well as atrophy of the brain, abnormal proliferations of cells and persistent biochemical changes in animals [5]; for the benzodiazepines [15, 16], for lithium see [17] for antidepressants see [18–22].

## 3. The syndrome of Chronic Brain Impairment (CBI)

The clinical effect of chronic exposure to psychoactive substances, including psychiatric drugs, produces effects very similar to those of close-head injury due to traumatic brain injury (TBI) [23] or the Postconcussive Syndrome [24]. Generalized or global harm to the brain from any cause produces very similar mental effects. The brain and its associated mental processes respond in a very similar fashion to injuries from causes as diverse as electroshock treatment [25] closed head injury from repeated sports-induced concussions or TBI in wartime, chronic abuse of alcohol and street drugs, long-term exposure to psychiatric polydrug treatment, and long-term exposure to particular classes of psychiatric drugs including stimulants, benzodiazepines, lithium and antipsychotic drugs.

Global or generalized brain impairments – those that involve the whole brain – look so much alike in their mental symptoms because the injured brain has only a limited repertoire of reactions. The healthy brain seems almost infinite in its capacity to create, so that the mental life of individuals with normal brains is very complex, rich and varied, and always unique. The wounded brain, and its associated mental

malfunctions, is much more limited and pedestrian. Its remaining richness and complexity depend on the existence of sufficient remaining brain function to allow for unique self-expression.

Based on these observations I have proposed the syndrome and diagnosis of Chronic Brain Impairment (CBI).[2] The specific cause of the CBI is added as a prefix, as in Alprazolam CBI, Antipsychotic Drug CBI, or Poly Psychiatric Drug CBI.[3] Other examples are ECT CBI, Polydrug Abuse CBI, and Concussive CBI.

### *3.1. Symptoms and characteristics of CBI*

Knowledge about CBI can help the clinician to identify the more subtle but potentially disabling effects of long-term exposure to psychiatric drugs and aid the clinician in determining the need to reduce or terminate drug treatment. CBI is the most frequent reason families become concerned about taking a family member off psychiatric drugs. CBI also leads individual patients to seek psychiatric help for themselves, but often they do not attribute their worsening condition to drug effects. Instead, they attribute it to "mental illness".

Psychiatric Drug CBI, like all CBI, is associated with generalized brain dysfunction and therefore manifests itself in an overall compromise of mental function. To help in identifying these deficits in clinical practice, the CBI syndrome can be divided into four symptom complexes which commonly present together:

(1) Cognitive dysfunctions which manifest in the early stages as short-term memory dysfunction and impaired new learning, inattention and difficulty concentrating.
(2) Apathy or loss of energy and vitality, often manifesting as indifference ("not caring") and fatigue. The individual commonly loses interest in creative activities, as well as other endeavors requiring higher mental processes, sensitivity to others, and spontaneity. The loss of empathy seen in these patients is probably an aspect of apathy as well as an aspect of the overall affective worsening.
(3) Emotional worsening (affective dysregulation) including loss of empathy, increased impatience, irritability, and anger, as well as frequent mood changes with depression and anxiety. This deterioration usually has a gradual onset over months or years so that it seems "normal" or becomes attributed to "stress," "mental illness," or "getting old".
(4) Anosognosia – lack of self-awareness of these symptoms of brain dysfunction. Whether it involves TBI, Alzheimer's disease, drug-induced tardive dyskinesia, or psychiatry drug CBI – patients commonly fail to identify their mental symptoms of brain dysfunction. Often someone other than the patient notices these changes. This is an aspect of anosognosia or the inability to recognize brain dysfunction in oneself [23].

As a result of these deficits, there is an associated reduction in the quality of life.

## 4. Comparison to dementia and Organic Brain Syndrome (OBS)

The cognitive criteria for CBI are less severe than those for dementia [26]. Only the most severe CBI patients will develop dementia symptoms such as apraxia, aphasia and agnosia; and any disturbances

[2]The phrase "chronic brain impairment" appears in various places in the literature on psychoactive drugs; but it has not been used as an overarching concept for a generic brain condition caused by multiple physical stressors, including long-term exposure to psychiatric drugs.

[3]Psychiatric Drug CBI and ECT-Induced CBI ([7], pp. 233–234) are aspects of the brain-disabling principle of biopsychiatric treatment ([7], Chapter 1).

of executive functioning would likely be very subtle. From a clinical standpoint, patients suffering from CBI are rarely diagnosed with dementia, even if they meet the criteria, because clinicians miss the subtle signs. Also, clinicians tend to think of dementia as a very severe and disabling disorder. In addition, clinicians are reluctant to diagnose dementia when it caused by psychiatric drug treatment.

Also in contrast to the diagnosis of dementia, the clinical criteria for CBI are more consistent with the actual clinical phenomenon associated with more subtle aspects of generalized or global brain dysfunction, including subtle cognitive deficits, apathy, affective dysregulation, and anosognosia. If a case of CBI becomes very severe, it would qualify as dementia. Because CBI is a specific syndrome, the severe condition should be diagnosed as CBI with dementia.

The concept of CBI also resembles the concept of organic brain syndrome (OBS). However, OBS is no longer used in the diagnostic system or in clinical practice [26]. When used in the past [27], it was not defined as a specific syndrome or a specific diagnosis with defined criteria. OBS was used to subsume a class of disorders that included specific diagnoses such as dementia or organic personality disorder. It did not have the nuance and broad spectrum of effects associated with CBI. I was not viewed as a unitary syndrome resulting from any physical harm to the brain.

### *4.1. Confounding factors*

When a patient has been exposed to years of psychiatric medication, other factors can cause or exacerbate Psychiatric Drug Induced CBI. The long-term impact of the individual's original psychological and emotional problems can induce apathy and emotional instability, and some degree of psychological denial that could be easily confused with anosognosia. However, there is no convincing evidence that primary psychiatric disorders, such as bipolar disorder or schizophrenia, can cause cognitive disorders or generalized brain dysfunction. In addition, CBI usually develops specifically in relationship to the persistent use of psychiatric drugs and can often be seen to worsen as doses are increased. Furthermore, CBI will usually begin to improve when the psychiatric drug dose is reduced. In contrast, pathology caused by a primary psychiatric disorder would be expected to worsen as the medication is reduced. After a syndrome consistent with CBI is identified, improvement with drug withdrawal is probably the most useful diagnostic criterion in distinguishing Psychiatric Drug Induced CBI from other disorders. The symptoms are partially or entirely relieved, and the quality of life improves.

Another potential confounding factor is exposure to other psychoactive substances. Many individuals who are exposed to long-term psychiatric medication will also be taking other prescribed medications that have psychoactive potential, including antihypertensive agents, pain medications, and anticonvulsants. Others will be exposed to psychoactive herbal remedies, alcohol or illegal drugs. A detailed clinical history is required to disentangle these drug effects. Again, improvement during psychiatric drug withdrawal is important diagnostically.

Many people in long-term psychiatric treatment, especially combat veterans, will also suffer from closed head injury. Also, any accompanying Post Traumatic Stress Disorder could become confused with CBI, since the symptoms overlap. Except for improvement on withdrawal from the psychiatric medications, CBI can be difficult to distinguish from closed head injury, without or without accompanying PTSD.

## 5. Patient awareness of CBI

Many patients desire to come off psychiatric drugs because they have some awareness of their deteriorating mental function. However, they almost never fully grasp how impaired they have become. This

lack of self-awareness of impaired brain function stems from two sources – psychological denial and neurologically-induced anosognosia. Psychological denial occurs when the individual has enough intact brain function to recognize symptoms of brain dysfunction but psychologically rejects this awareness and utilizes denial. Anosognosia is physically caused when brain injury impairs the capacity for this aspect of self-awareness [8, 9, 23]. Obviously, the two phenomena can be difficult to separate.

Drug-induced anosognosia when severe can become intoxication anosognosia or medication spellbinding in which an individual can develop dangerous behavioral patterns, including suicide and violence, that would not otherwise have occurred [7, 28]. This risk must be taken into account by the prescriber, the therapy team, the patient and the patient's support network, especially during dose changes and withdrawal.

### *5.1. Frequency of CBI*

Psychiatric Drug CBI was relatively rare in the early decades of my career in psychiatry (I graduated medical school in 1962) when far fewer children and teens were treated with psychiatric drugs, when polydrug treatment was looked upon much more critically, when doctors rarely encouraged patients to stay on psychiatric drugs for the remainder of their lives, and when potent antipsychotic drugs were not given out so freely to patients with no signs whatsoever of psychosis. Undoubtedly, the widespread use of alcohol and illegal drugs, often taken in combination with prescription drugs, has helped turn CBI into an epidemic.

It is difficult to estimate what percentage of patients will develop CBI after years of exposure to psychiatric drugs. In my clinical experience, nearly all patients who remain on these chemical agents for many years will develop some symptoms of CBI. If the patient is taking multiple psychiatric drugs for years at time, in my experience CBI is always marked.

The most noticeable effects are short-term memory dysfunction and a loss of interest in daily activities, hobbies, creative endeavors, and sometimes family and friends. The clinician can inquire about creative activities requiring higher mental function, sensitivity to others, and spontaneity – such as art work, writing, music, close friendships, and sexual relations. Individuals exposed long-term to psychiatric drugs will commonly report a loss of interest, intensity or satisfying engagement in these activities. Sometimes they will deny their losses which are nonetheless confirmed by family members and loved ones.

### *5.2. Recovery from CBI*

Recovery from CBI usually begins early in the withdrawal process and can continue for some time, even years, after stopping all psychiatric medication. As the number of drugs and their dosages are reduced, patients show improvements in memory, engagement in activities, and mood stability. Because of anosognosia, the patient may not recognize the improvements as quickly or thoroughly as the prescriber, therapist, or family; but it would be unusual if the patient fails to notice or acknowledge any positive changes early in the drug withdrawal process.

If the patient does not begin displaying significant improvement in CBI symptoms during the drug withdrawal process, the clinician should suspect the presence of another underlying medical disorder, and take appropriate steps to ensure adequate medical evaluation. Psychiatric Drug CBI can be confused with or worsened by any additional disorders that impair brain function. The covert use of alcohol or illegal drugs can impair the withdrawal process.

While further medical evaluation is conducted, the medication withdrawal should be continued, if possible, in order to clarify the clinical diagnosis and provide optimum conditions for healing any underlying physical disorder. Many underlying disorders, including neurological disorders that impair brain function, are apt to be significantly worsened by continued exposure to psychoactive substances, including psychiatric drugs.

Young children and teenagers often seem to experience full recovery from CBI despite years of exposure. It is imperative to prevent the long-term exposure of children and youth to psychiatric medications, all of which can impede learning and emotional development, and injure the brain. In my clinical experience, children and teenagers are especially resilient after removal from the offending agents.

Adult patients are more likely to experience continued subtle CBI difficulties with memory, attention or concentration after withdrawal from years of exposure to psychiatric medication; but even in the presence of residual symptoms, they can lead fulfilling lives.

Of course, there is also a risk of psychiatric relapse. However, even if this occurs, improvement in the patient's CBI may be worth it to the patient and the family. In addition, these "relapses" are often due to delayed withdrawal reactions manifested, for example, as the return of depression a few weeks after antidepressant withdrawal or the return of manic symptoms within weeks after withdrawal from lithium. In this case, instead of reinstituting a starting dose of medication, it may be sufficient to provide drug-free psychotherapy or to extend the withdrawal somewhat longer with small doses of the medication.

Persistent multi-drug exposure, high drug doses, length of exposure, and older age can contribute to the risk and severity of CBI. The best way to prevent CBI is to use psychiatric medications sparingly and to limit exposure to the shortest possible length of time.

### *5.3. Treatments for CBI*

The initial and only effective treatment for CBI is complete withdrawal from all psychiatric drugs as well as all other psychoactive substances. During the withdrawal process, it is important to establish healthy living practices in regard to good nutrition (no special diets), moderate exercise, and sufficient rest and sleep.

Patients should be discouraged from turning to additional psychoactive substances, including herbs or natural remedies. They can worsen the CBI and interfere with a successful withdrawal process. The covert use of alcohol and illegal drugs will also impair withdrawal.

Close monitoring of the patient during drug withdrawal is required. In addition, the drug withdrawal process should be accompanied by supportive psychotherapy for both the patient and significant others who can provide support during the sometimes difficult process. Couples or family therapy is potentially the most effective. It can help the uninjured partner understand the struggle to triumph over brain dysfunction and strengthen the relationship in supportive ways for both partners. Cognitive-behavioral Therapy (CBT) can be useful in promoting better ways to think of responsibility and self-determination but nothing is more important than supportive relationships when brain function is impaired.

The patient's subjective experience is the best gauge for pacing the withdrawal process. Utilizing a person-centered approach [29], it is best to start with a small dose reduction, and then to step-by-step make reductions dependent upon how the patient is responding. To reduce fear and anxiety, patients must feel in charge of the rate of the withdrawal process.

Any therapy that can produce emotional stress, such as insight therapy that explores childhood trauma, or couples therapy that deals with severe conflicts, should be delayed until the patient is able, willing and eager to take on these challenges.

Programs for cognitive rehabilitation are probably less effective than encouraging the individual to engage in useful, pleasurable and stimulating physical and mental activities. Encourage individuals with CBI to rediscover activities that they once loved. Frequently, they have given them up.

A recurrence or worsening of the individual's psychiatric disorders is a major concern during withdrawal, especially in regard to individuals who have been made vulnerable by CBI. In my own experience, however, judicially and slowing removing long-term psychiatric drugs – along with appropriate psychotherapy – usually helps in recovery from psychiatric disorders.

After medication withdrawal, patients often declare, "I've gotten my life back. I'm myself again!" Family members often feel that they have regained the husband, wife or child that they used to know and love before the adverse medication effects set in. The work of psychiatric drug withdrawal, while sometimes difficult and hazardous, can be very gratifying to the clinician and extremely empowering to the patient and family.

## 6. Conclusion

By learning to recognize Psychiatric Drug-Induced Chronic Brain Impairment (CBI), clinicians can enhance their ability to identify patients who need to be withdrawn from long-term psychiatric drug treatment. CBI symptoms are the main reason why patients and their families seek professional help in withdrawing from psychiatric medications.

The symptoms of this syndrome include (1) Cognitive deficits, often first noticed as short-term memory dysfunction and impaired new learning, and difficulty with attention and concentration; (2) Apathy, indifference or an overall loss of enjoyment and interest in life activities; (3) Affective dysregulation, including emotional lability, loss of empathy and increased irritability; (4) Anosognosia or a lack of self-awareness about these changes in mental function and behavior.

Most patients begin to recover from CBI early in the withdrawal process. Many patients, especially children and teenagers, will experience complete recovery. Others may recover over a period of years. Even when recovery is incomplete, or psychiatric relapses occur off the medication, most patients remain grateful for their improved CBI, and wish to remain on reduced medication or none at all.

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