

# Anticholinergic Use and Misuse in Psychiatry: A Comprehensive and Critical Review

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## Abstract

Anticholinergic medications such as Trihexyphenidyl; Biperidine are widely prescribed to prevent or to treat extrapyramidal side effects produced by neuroleptic drugs. Concomitant use of anticholinergic drugs is more common with the first generation antipsychotic medications. There is a considerable body of data suggesting that anticholinergic drugs have a potential of abuse. In this article, we review the psychiatric use, mechanism of action and the abuse of each anticholinergic drug.

**Keywords:** Acetylcholine receptors; Anticholinergic drugs; Schizophrenia; Antiparkinsonian drugs; Trihexyphenidyl; Artane; Biperidine; Akineton; Benztropine; Cognitine; Procyclidine; Kemadrin; Abuse and misuse

## Introduction

Anticholinergics are regularly used in psychiatric practice to counteract the extrapyramidal symptoms secondary to antipsychotic drugs [1]. Among the most frequently used in psychiatry are Trihexyphenidyl; Biperidine; Benztropine; and the Procyclidine.

Anticholinergic abuse, although thought to be uncommon, has been reported in several clinical settings primarily in patients with severe mental illness where the prevalence of misuse could reach 34 percent [2]. Studies revealed that the purpose of abuse is to achieve a euphoric state and to enhance social skills [3].

This review aims to highlight existing data about the pattern of utilization, the misuse potential of each anticholinergic drug, and the prevalence of abuse.

## Methods

Search was conducted using MEDLINE (via PubMed; 1960 till 2016), and using the principal keywords:

Acetylcholine receptors, Anticholinergic drugs, first generation and second generation antipsychotics, schizophrenia, antiparkinsonian drugs, Trihexyphenidyl, Artane, Biperidine, Akineton, Benztropine, Cognitine, Procyclidine, Kemadrin, use, abuse and misuse.

An initial broad strategy was undertaken to find all review articles, case reports, and controlled studies. This was followed by scanning the bibliographies of all identical trials for additional studies.

## Psychiatric Use of Anticholinergic Drugs

Anticholinergic drugs were mostly used to reverse extrapyramidal symptoms [1] resulting from antipsychotic drugs used in the treatment of schizophrenia.

Schizophrenia is the most baffling of psychiatric syndromes and one of the most debilitating medical conditions, characterized by positive, negative, cognitive and affective symptoms, with a worldwide prevalence of approximately 1% [4].

The fortuitous discovery of chlorpromazine's efficacy in 1952 was soon followed by the description of its propensity to produce extrapyramidal side effects [5]. Soon after, it was postulated that extrapyramidal side effects are indicators of the therapeutic efficacy. Bleich et al. suggested that the development of extrapyramidal symptoms is necessary for the antipsychotic efficacy of neuroleptic drugs [6]. It was the advent of clozapine, and the testing of its antipsychotic propriety free of Parkinson symptoms that invalidated this postulate.

Patients treated by antipsychotic drugs, and experiencing extrapyramidal side effects can be more inclined to quit medications due to the unease they feel from tremors, rigidity and dyskinesia. This poor compliance can even be more exacerbating for their psychotic symptoms [7].

For this reason, anticholinergic drugs are introduced to prevent or to treat extrapyramidal side effects [1] that are more pronounced with first generation antipsychotics-known for their high propensity for parkinsonian side effects [8] than with second generation antipsychotics (Table 1) [9].

## Pharmacology of Anticholinergic Drugs

Acetylcholine, an organic chemical that functions in the brain and body as neurotransmitter, has multiple physiological functions in the peripheral and central nervous system [13]. Acetylcholine exerts its effect by binding two major subtypes of receptors: the metabotropic muscarinic receptors [14] and the inotropic nicotinic receptors [15].

The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons [16]. Blocking dopamine receptors by antipsychotics alter this balance, causing a relative excess of cholinergic influence, resulting in extrapyramidal motor effects [17]. If cholinergic activity is also blocked by anticholinergic drugs, a new nearly more normal balance is restored and extrapyramidal side effects are minimized [16].

Highest propensity for EPS



Lowest propensity for EPS

High potency first generation antipsychotics: Haloperidol, Fluphenazine, Pimozide, Perphenazine
Mid potency: First generation: Loxapine, Perphenazine; Second generation: Risperidone, Paliperidone
Low potency first generation: Chlorpromazine, thioridazine
Olanzapine, Ziprazidone, Abilify
Quetiapine
Clozapine

**Table 1:** Propensity for Extrapyramidal Side effects (EPS) among different antipsychotic drugs [10-12].

On the other hand, anticholinergic drugs act also as a potent indirect dopamine agonist [16] in the limbic system, which is a set of interconnected brain structures including the nucleus accumbens and the ventral tegmental area involved in motivation, learning, memory and reward. This can in part explain the misuse potential of anticholinergic drugs in both psychiatric and non-psychiatric patients.

### Trihexyphenidyl (Artane; Benzhexol)

The exact mechanism of action of Trihexyphenidyl in reducing the extrapyramidal side effects of antipsychotic medications is poorly understood. What is known that it binds with high affinity to M<sub>1</sub> Muscarinic receptors [18] and possibly with Dopamine receptor [19]? Daily dosage usually ranges from 5-15 mg in 2 or 3 divided doses (Table 2).

While the blockade of the muscarinic peripheral receptors results in reversible and minor side effects such as dryness of the mouth, drowsiness, constipation, and blurred vision; the blockade of the central nervous system receptors yields major psychiatric symptoms such as euphoria, visual and auditory hallucinations [20]. In 1960, Oliver Sacks, a neurologist, took a large dose of Trihexyphenidyl and shared his state of mind and perceptual alteration symptoms [21]. He reported hallucinations including seeing and chatting two close friends arrived and feeling euphoric.

Concurrently, Bolin presented the first case of abuse of anticholinergic drugs in a 32 year old woman admitted to a psychiatry ward for Trihexyphenidyl induced toxic psychosis prescribed at a dose of 2 mg daily 4-6 times for relief of a severe torticollis. The patient had progressively increased the dose reaching 30 mg within a month seeking a euphoric state and a “sense of well-being” [22].

This first recorded case was followed by a series of reports of misuse and abuse from different areas of the world.

In Great Britain, Trihexyphenidyl was used by young people for its hallucinogenic properties [23]. Moreover; a recent survey conducted in the 107 largest Brazilian cities showed that the lifetime prevalence of anticholinergic drug use, mostly Trihexyphenidyl reached 1.1% in the sample aged 12-65 years [24]. In 37 patients diagnosed with drug abuse based on the diagnostic and statistical manual of mental

disorders (DSM IV) in Sao Paolo, Nappo et al. reported that Trihexyphenidyl abusers were in majority single unemployed men with poor socio-economic status and no specific age for initiating consumption [25].

In 2000, Buhrich et al. reported a prevalence of anticholinergic abuse of 34% in fifty patients with serious mental illness in Sydney, Australia. The primary reason for misuse was to get “High”, yet these study didn’t reveal why Trihexyphenidyl, the most stimulating anticholinergic drug was the most widely abused [2]. This was replicated by Zemishlany et al. in 214 patients diagnosed with schizophrenia according to the DSM-IV criteria, where they found that Trihexyphenidyl was the sole anticholinergic drug to be used in doses higher than those prescribed. However, its incidence was 6.5% which is by far much lower than what is reported in the Buhrich’s study [26].

Substance abuse is more common in patients with schizophrenia (47%) as compared to 17% in the general population [27]. This misuse may be an attempt to relieve psychotic symptoms or to override the side effects of psychotropic medications. In 2001, the prevalence of Trihexyphenidyl abuse was 2.1% in 3028 patients (86.2% had a neuroleptic prescription). The dosage of Trihexyphenidyl was as high as 28 mg/day and most of the individuals were young men who also abused other drugs such as Buprenorphine or Flunitrazepam [28].

Moreover, several case reports predating the aforementioned studies tackled the subject of Trihexyphenidyl abuse.

Macvicar in 1977 presented a case of a 30 year old paranoid schizophrenic patient who had been taking 4 mg of Trihexyphenidyl per day to relieve a dystonic reaction to Haloperidol. He started to increase the dose progressively reaching 15 mg/day, enjoying the facilitated talkativeness and friendliness [29].

Rubinstein reported 8 cases of antiparkinsonian drug abuse; five of them included oral Trihexyphenidyl [30].

Lo et al published a case of a chronic schizophrenic patient who abused Trihexyphenidyl up to 200 mg/day. Upon discontinuation, he developed anxiety, and feigned extrapyramidal symptoms in order to receive anticholinergic injections.

Medications	Recommended dose	Half-life
Trihexyphenidyl	Initial 1 mg/day. Increase as necessary to a usual range 5-15 mg/day in three divided dose	33 h

Benztropine	1-4 mg, 1-2 times/day	7 h
Biperidine	2 mg, 3-4 times/day Maximum dose 16 mg/day	18 h
Procyclidine	Initial dose 2.5 mg, 3 times/day Maximum dose 30 mg/day	12 h

**Table 2:** The recommended dose and the half-life of each anticholinergic drug [31,32].

### The other anticholinergic drugs

Albeit Trihexyphenidyl was the most commonly misused [33] of the anticholinergic drugs, none of the others seem to be free from the potential of abuse.

In 1974 Woody and O'Brien presented 6 cases of anticholinergic toxic psychosis following the administration of Benztropine, the six were taking more than the recommended dose of the medicine (Table 2) [34]. To further alert physicians on the potential of abuse of Benztropine, Craig et al presented two cases coming to the emergency department for bizarre behavior [35]. After receiving intravenous Physostygmine to relieve the anticholinergic symptoms of dry mouth, urinary retention, and altered mental status and within 5 min, patients recovered and admitted using high dose of Benztropine.

The data regarding the potential risk of dependence based upon the reinforcing and rewarding properties of Biperidine is controversial. At a time, the experimental dose used on rats in the conditioned place preference [36] and the Norway study involving 73724 patients on Biperidine or Orphenadrine to treat either an extrapyramidal side effect or a parkinsonian disease showed no such risk [37]. On the contrary, Martinez et al suggested otherwise by publishing a case of a 47 year old man admitted to a psychiatric ward for a detoxification of Biperidine dependence, having been taking up to 50 mg of Biperidine a day. Withdrawal symptoms of anxiety, restlessness, and tremors upon discontinuation were reported [38].

### Discussion

It is clear from the aforementioned reports in this review that anticholinergic drugs, more particularly Trihexyphenidyl, can be more abused than the other Antiparkinsonian.

However, it is still poorly understood if this class difference is attributable to the stimulating properties of Trihexyphenidyl as compared with the other compounds, or simply because the former is the most commonly prescribed of all anticholinergics [33]. The abusers were predominantly single, males, unemployed, of poor socio-economic status, and suffering from a more severe mental illness. As a matter of fact, the prevalence of abuse in this latter group of patients can reach 34% [2]. The aim of the abuse is to achieve a high state reducing the depressive and negative symptoms secondary to the cholinergic system hyperactivity [39].

However tolerance to the euphoric effect builds up rather quickly, driving patients to progressively increase the dose that in turn, may occasionally result in a toxic reaction exhibited by a hostility and suspicious behaviour [35].

Abuse should always be suspected in outpatients who ask for additional supplies of anticholinergic drugs. Surprisingly, the

prevalence of abuse in drug addicts who are not using antipsychotic drugs remains relatively low [40].

The common final pathway for the reinforcing effect of abused drugs has been repeatedly postulated to be the product of the mesolimbic dopaminergic system including the ventral tegmental area, the nucleus accumbens, and the prefrontal cortex.

Through the blockade of the muscarinic receptors, anticholinergic drugs inhibit dopamine reuptake and storage, accounting for the euphoric and hallucinogenic effects encountered with their use [41]. Nevertheless, if all anticholinergic drugs carry a risk of abuse, no putative pathophysiological mechanism explaining this effect has yet been found.

There are various measures that can be followed to reduce the risk of abuse. Firstly, anticholinergic consumption and prescription should be carefully monitored. Moreover labeling these drugs with precautions of abuse and misuse may raise the sense of awareness and act as a reminder for physicians and patients about the risk of overconsumption. Finally, shifting when possible towards second generation antipsychotics could contribute to less extrapyramidal side effects, and hence cutting down the use of anticholinergic drugs.

### Conflict of Interest

There is no conflict of interest to declare. This work is not supported or funded by any drug company.

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