Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential

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Abstract
Bipolar affective disorder is often poorly controlled by prescribed drugs. Cannabis use is common in patients with this disorder and anecdotal reports suggest that some patients take it to alleviate symptoms of both mania and depression. We undertook a literature review of cannabis use by patients with bipolar disorder and of the neuropharmacological properties of cannabinoids suggesting possible therapeutic effects in this condition. No systematic studies of cannabinoids in bipolar disorder were found to exist, although some patients claim that cannabis relieves symptoms of mania and/or depression. The cannabinoids Δ⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD) may exert sedative, hypnotic, anxiolytic, antidepressant, antipsychotic and anticonvulsant effects. Pure synthetic cannabinoids, such as dronabinol and nabolone and specific plant extracts containing THC, CBD, or a mixture of the two in known concentrations, are available and can be delivered sublingually. Controlled trials of these cannabinoids as adjunctive medication in bipolar disorder are now indicated.

Keywords
bipolar disorder, cannabidiol, cannabinoids, cannabis, CBD, depression, dronabinol, mania, nabilone, tetrahydrocannabinol, THC

Introduction
The treatment of bipolar affective disorder (BAD) remains problematic despite several guidelines or consensus statements (Sachs et al., 2000; Geddes and Goodwin, 2001; Goodwin, 2003; Lloyd et al., 2003). The mean time to relapse after the first episode is 5 years (Geddes et al., 2003) and periods of remission shorten as the illness progresses, regardless of treatment. Most patients with BAD are prescribed a combination of drugs, all of which have their disadvantages. Lithium, although efficacious, has limited effectiveness because of low acceptance and occurrences of mania on withdrawal. Many anticonvulsants can produce unacceptable side-effects (Porter et al., 1999; Ashton and Young, 2003). Sodium valproate, the most commonly prescribed mood stabilizer, carries risks in women of childbearing age (Committee on Safety of Medicines, 2003; Goodwin and Sachs, 2004). Lamotrigine, although effective in bipolar depression, requires careful dosage control to prevent skin complications, which may prove to be serious. Conventional antidepressants and electroconvulsive therapy can induce mood elevation, which may progress to rapid mood cycling. Antipsychotic drugs have many undesirable effects and the atypical antipsychotics quetiapine, olanzapine and risperidone have all been reported to induce mania in some cases (Mishra et al., 2004). Psychosocial measures have been shown to complement medication, but they remain at an early stage of development and their widespread use is limited by available resources.

Thus, there is a clear need to explore new ways of managing bipolar disorder. Patient reports and observations, backed by known pharmacology, suggest that the cannabis derivatives Δ⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD) may have mood stabilizing properties. The present study aimed to review the evidence for this. The use of controlled substances in medicine is...
widespread, especially in children with psychological difficulties and in pain management. Nevertheless, the consequences of extending the use of controlled substances need careful consideration.

It is well known that there is a high prevalence of comorbid drug abuse in people with BAD (Brown et al., 2001). A 61% lifetime prevalence of substance abuse in Bipolar I patients and 48% in Bipolar II patients has been reported compared to 6% in the general population (Regier et al., 1990). Some studies have provided data on individual drugs that are abused by these patients (Estroff et al., 1985; Miller et al., 1989; Regier et al., 1990; Marken et al., 1992; Mueser et al., 1992; Sonne et al., 1994; Winokur et al., 1998). The results indicate high rates of lifetime use of cannabis (30–64%) and stimulants (amphetamines 31–39%, cocaine 15–39%) and lower rates for opiates (6–25%). The extent to which bipolar patients use cannabis as self-medication is not clear, although anecdotal reports suggest that some patients find it alleviates both depression (Gruber et al., 1996) and mania (Grinspoon and Bakalar, 1998). Although cannabis can cause adverse effects, including psychosis and mania, some cannabinoids have properties that could be of value in psychiatric disorders, and a literature review was therefore undertaken to investigate their therapeutic potential in bipolar affective disorder.

**Methods**


In addition, Medline reviews and investigations of pharmacological, psychiatric and therapeutic effects of cannabis/cannabinoids (1970–2003) were consulted and a manual searching of all relevant articles was performed.

**Results**

The literature search revealed no systematic studies of the therapeutic use of cannabis or cannabinoids in BAD, although there are several anecdotal reports. Grinspoon and Bakalar (1998) described five cases in which cannabis appeared to alleviate mania. For example, one woman with BAD quoted in their report chose cannabis over alcohol to control her manic behaviour: ‘A few puffs of this herb and I can be calm … this drug seems harmless compared to other drugs I have tried, including tranquillisers and lithium’. A husband, describing his wife with BAD said: ‘My wife functions much better when she uses marijuana. When she is hypomanic, it relaxes her, helps her sleep, and slows her speech down. When she is depressed and would otherwise lie in bed all day, the marijuana makes her more active … Lithium is also effective, but it doesn’t always keep her in control’.

Personal observation of a patient attending the local outpatients also indicated an apparent antimanic effect of cannabis. The patient was a 39-year-old male who had been diagnosed 10 years previously as having BAD. His illness mainly took the form of manic episodes for which he had a history of five hospital admissions. These episodes were difficult to control because the patient was intolerant of antipsychotic drugs, including quetiapine and risperidone, and non-compliant with lithium and sodium valproate. Diazepam controlled his symptoms but he often used up his 2-week prescription for 30 mg daily in 1 week.

A recent manic episode was associated with a severe behaviour disturbance involving a further possible detention order. The psychiatrist was called for a home visit, which he made some hours later. To his surprise, he found the patient calm, almost serene, sitting tranquilly in an armchair smoking a cannabis ‘spliff’. (He offered the psychiatrist one of the same, which was declined). It was clear that the cannabis was responsible for the rapid change in the patient’s behaviour. He maintained that, over the years, he had taken mainly cannabis, sometimes moderate amounts of alcohol, occasionally ‘street’ benzodiazepines, and infrequently heroin to regulate his mood.

Gruber et al. (1996) described five cases in which marijuana appeared to produce a direct antidepressant effect. Three of these patients had BAD and all but one found that marijuana relieved their depression better than standard antidepressant drugs. Two surveys of medicinal cannabis use in California, where this use is legalized, showed that 15–27% of patients were prescribed it for mood disorders, including depression, post-traumatic stress disorder, BAD and attention deficit disorder resistant to conventional pharmacotherapy (Gieringer, 2003).

It is noteworthy that, in the anecdotal reports, cannabis was not taken for the ‘high’ sought by recreational users and it is possible that its effects are different when taken in subeuphoric doses for medical reasons, such as in multiple sclerosis or pain conditions (Randall, 1991; Hodges, 1993). The effects are most probably due to cannabinoids present in cannabis smoke, including Δ9-THC, CBD and possibly others, which have been less studied. Patients’ accounts and the advances in the understanding of cannabinoid physiology suggest that they may have a therapeutic potential in BAD (Pertwee, 1999a,b).

**Pharmacological basis of cannabinoid effects: the endocannabinoid system**

**THC and cannabinoid CB1 receptors** THC is the major psychoactive agent present in cannabis, and its primary metabolite, 11-OH-THC, is even more potent (Maykut, 1985; McPartland and Russo, 2001). These cannabinoids are agonists of endogenous cannabinoid CB1 receptors that are present in the brain, spinal cord and peripheral nerves. CB1 receptors are widely distributed throughout the brain (Table 1) and are present in the cerebral cortex, including the cingulate cortex, hippocampus, basal amygdala, corpus striatum and other areas possibly involved in the pathophysiology of BAD and its emotional and cognitive components (Drevets et al., 1997; Strakowski et al., 1999; Altshuler et al., 2000; Phillips et al., 2001).
Cannabinoids in bipolar disorder

Table 1 Localization of cannabinoid CB₁ receptors

<table>
<thead>
<tr>
<th>Density</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very dense</td>
<td>Basal ganglia — globus pallidus, substantia nigra pars reticulata, entopeduncular nucleus</td>
</tr>
<tr>
<td></td>
<td>Cerebellum — molecular layers</td>
</tr>
<tr>
<td>Dense</td>
<td>Cerebral cortex* — layers I and VI</td>
</tr>
<tr>
<td></td>
<td>Hippocampus — CA pyramidal cells</td>
</tr>
<tr>
<td></td>
<td>Corpus striatum — caudate putamen</td>
</tr>
<tr>
<td>Moderate</td>
<td>Hypothalamus* — Basal amygdala*</td>
</tr>
<tr>
<td></td>
<td>Central grey substance — Nucleus of solitary tract</td>
</tr>
<tr>
<td></td>
<td>Spinal cord — Peripheral nerve terminals</td>
</tr>
<tr>
<td>Sparse</td>
<td>Thalamus — Pons and Medulla</td>
</tr>
<tr>
<td></td>
<td>Some non-neural tissues, including spleen and testes</td>
</tr>
</tbody>
</table>

*Receptor density in the cingulate cortex, hypothalamus and amygdala is relatively greater in the human brain than in the same areas of rat and monkey brain (Herkenham, 1995; Pertwee, 1997).

CB₁ receptors belong to a family of G-protein coupled receptors that includes receptors for aminergic neurotransmitters (noradrenaline, dopamine, serotonin and acetylcholine) and act through second messenger systems. CB₂ receptors are similar to CB₁ receptors but are present mainly in immune cells in the periphery and are not considered further here.

Activation of the CB₁ receptor (Fig. 1) inhibits adenylate cyclase and decreases the production of cAMP (3,5-adenosine monophosphate) (Pertwee, 1997), an action which affects many intracellular processes and ultimately affects intracellular neurotransmission (Shiloh et al., 1999). CB₁ receptors also modulate transneuronal ion channels. They are negatively coupled to calcium channels (N and P/Q type) and inhibit the inward flow of calcium ions, decreasing the release of neurotransmitters, either excitatory or inhibitory, at presynaptic nerve terminals (Pertwee, 1997). At the same time, CB₁ activation enhances the outward flow of potassium ions (through A-type potassium channels), a G-protein coupled event that may also depend on inhibition of cAMP production (Deadwyler et al., 1995). The result is inhibition of neuronal depolarization, decreased action potential generation and hence reduced impulse propagation.

**CBD and anandamides**

The endogenous ligands for cannabinoid receptors, both CB₁ receptors in the nervous system and CB₂ receptors in peripheral tissues, are a family of arachidonic acid derivatives, sometimes termed endocannabinoids (Pertwee, 1999a,b). The two that appear to be of most physiological importance are arachidonylethanolamide (anandamide) and 2-arachidonylglycerol (2-AG). Anandamide is present in the brain in the same areas as CB₁ receptors. It is enzymatically synthesized in cell membranes, binds to CB₁ receptors (Van der Stelt and Di Marzo, 2003) and, in animal models, shows many of the actions of THC (Stein et al., 1996; Martin and Cone, 1999). However, unlike THC, the effects of anandamide are short-lived, lasting less than 15 min after intravenous injection in the rat (Stein et al., 1996) because it is rapidly inactivated by enzymatic hydrolysis and removed from its site of action by neuronal uptake mechanisms (Joy et al., 1999; Pertwee, 1997, 1999b; Piomelli et al., 2000; Alger, 2004). In addition, anandamide is synthesized and released at discrete loci on demand by neural activity or depolarization of postsynaptic membranes and then acts retrogradely as an agonist on presynaptic CB₁ receptors (Howlett, 1995; Pertwee, 1997; Ameri, 1999; Joy et al., 1999; Van der Stelt and Di Marzo, 2003; Alger, 2004).

CBD binds only minimally to CB₁ receptors and is usually described as non-psychoactive. However, the clinical observations described below suggest that it has antipsychotic, anxiolytic, anti-convulsant and other psychological effects (Zuardi et al., 1995; Mechoulam et al., 2002). Its mode of action is not fully understood but CBD has recently been shown to block the reuptake of...
anandamide (Bisogno et al., 2001) and to inhibit its enzymatic
hydrolysis (Mechoulam et al., 2002). CBD also reduces the
hydroxylation of THC to its more psychoactive metabolite, 11-OH-
THC (McPartland and Russo, 2001). It has been shown to inhibit
serotonin reuptake and to increase catecholamine activity in rat
brain synaptosomes (McPartland and Russo, 2001), an action also
shown by anandamide (Steffens and Feuerstein, 2004). In addition,
CBD is a potent antioxidative agent and is protective against gluta-
mate toxicity, an action which is not affected by cannabinoid
receptor antagonists (Mechoulam et al., 2002). The possible con-
tribution of each of these actions to the psychological effects of
CBD is not clear.

The discovery of endocannabinoids and the realization that
these are the biological ligands of cannabinoid receptors has
opened a whole new vista in cannabinoid pharmacology. A system
of cannabinoid receptors and endocannabinoids appears to modu-
late many important physiological processes (Di Marzo et al.,
1998). These processes have yet to be clearly defined but evidence
is already accumulating that endocannabinoids are involved in the
modulation of brain reward systems (Gardner, 1999), mood, anxiety
and sleep (Musty et al., 1995), pain (Pertwee, 2001), cognition
and memory (Terranova et al., 1995, 1996), appetite (Williams and
Kukham, 1999; Di Marzo et al., 2001), endocrine activity
(Mendelson and Mello, 1999), cardiovascular regulation (Randall
and Kendall, 1998) and other vital functions (Musty et al., 1995;
Ameri, 1999). The basic function of the endogenous system
appears to be the regulation of interneuronal signalling, involving
complex interactions with many neurotransmitters and neuromod-
ulators, including monoamines, acetylcholine, opioids, GABA and
glutamate (Ameri, 1999).

Psychological effects of THC

The psychological effects of cannabis and THC have been
described by many authors (Paton and Pertwee, 1973; Ashton,
1999a; Johns, 2001). It is important to note that many of these are
biphasic and bidirectional, depending on dose, mode of administra-
tion, environment, expectation, personality, degree of tolerance and
other individual factors, as well as time-frame (Paton and Pertwee,
1973; Ashton et al., 1981; Ashton, 1999b). Thus, acute effects in
normal subjects can include euphoria or dysphoria, relaxation or
anxiety, excitation followed by sedation, heightened
perception followed by perceptual distortion, and increased motor
activity followed by incoordination. Synthetic THC (dronabinol)
and nabilone, a synthetic cannabinoid related to THC, exert similar
actions depending on dosage and the other factors mentioned
above. In healthy subjects under placebo-controlled laboratory
conditions, THC (5 mg and 10 mg smoked in herbal cigarettes) was
shown to produce relaxation with decreased subjective ratings of
anxiety, tension and depression (Ashton et al., 1981). However,
D’Souza et al., 2004) recently found that intravenous infusions of
THC (2.5 mg and 5 mg) produced mild and transient schizophrenia-
like symptoms, anxiety, detachment, perceptual distortion and
cognitive impairment.

Patients using cannabis or synthetic THC compounds in mod-
erate doses for chronic pain conditions or multiple sclerosis have
reported improvement of mood and increased general well-being
and mental health, as well as alleviation of their other symptoms
(Martyn et al., 1995; Notcutt et al., 1997; Ashton, 1999b; Williams
and Evans, 2000; Wade et al., 2003; Svendsen et al., 2004). A few
controlled studies have shown anxiolytic effects of nabilone in
some patients (Glass et al., 1980; Fabre and McLendon, 1981;
Ilaria et al., 1981) and an antidepressant effect of THC in cancer
patients (Regelson et al., 1976; Russo et al., 2003).

Many of the adverse effects of cannabis (usually attributed to its
THC content) result from relatively high dose or chronic use.
Cannabis can cause an acute psychosis in previously normal indi-
viduals, but those with mental illness are more vulnerable (Johns,
2001). Such reactions are dose-related and appear to be becoming
more common with the present-day recreational use of potent
cannabis varieties such as ‘skunk’ and netherweed (Wylie et al.,
1995). Heavy cannabis use can also lead to an acute functional psy-
chosis with marked hypomanic features (Rottenburg et al., 1982;
Johns, 2001). In patients with BDD, the duration of cannabis use is
associated positively with the duration of manic, but not depres-
sive, episodes (Strakowski et al., 2000) and substance abuse in
general appears to increase the severity of the illness (Cassidy et
al., 2001) and to increase suicide rate (Dalton et al., 2003).

Cannabis is a well-known risk factor for schizophrenia and may
precipitate the illness in genetically predisposed individuals
(Johns, 2001). It aggravates positive symptoms in schizophrenia
and may antagonize the effects of antipsychotic drugs (Negrete
and Gill, 1999). A large number of studies, as reviewed by Arsenault
et al. (2004) and Macleod et al. (2004), have implicated a dose-
related association between the use of cannabis in childhood and
adolescence with later development in young adulthood of schizo-
phrenia, depression, violence and antisocial behaviour, use of other
illicit drugs, lower educational attainment, and psychological
distress. Whether or not these associations are causal are debated
by the above authors.

Psychological effects of CBD

There is some evidence that CBD, which constitutes up to 40% of
cannabis extracts, has anxiolytic, hypnotic, antipsychotic and anti-
convulsant actions (Zuardi and Guimaraes, 1997; Mechoulam et
al., 2002). CBD antagonizes the anxiety, intoxication liability and
psychotic-like symptoms produced by high doses of THC in normal
subjects (Zuardi et al., 1982; Russo, 2003) and has similar
anxiolytic effects to diazepam in a simulated public speaking test
(Zuardi and Guimaraes, 1997). Anxiolytic effects have also been
demonstrated in animal models, including the behaviour of rodents
on the elevated plus maze (Guimaraes et al., 1997). CBD also has
similar anti-convulsant action of THC in normal subjects (Zuardi et
al., 1982; Russo, 2003) and has similar
anxiolytic effects to diazepam in a simulated public speaking test
(Zuardi and Guimaraes, 1997). Anxiolytic effects have also been
demonstrated in animal models, including the behaviour of rodents
on the elevated plus maze (Guimaraes et al., 1997). In this test, the
action of CBD, administered alone, was dose-dependent and
biphasic, similar to many other cannabinoid effects (Sulcova et al.,
1998). Biphasic hypnotic effects in rats have also been demonstrated
(Monti, 1997) and CBD significantly increased sleeping time
compared to placebo in insomniacs (Carlini and Cunha, 1981).

Antipsychotic effects of CBD were suggested by the observation
that it acted in a similar way to haloperidol in animal tests predic-
tive of antipsychotic activity (Zuardi et al., 1991, 1995). A placebo-
controlled case study of a patient with schizophrenia who was
Intolerant of haloperidol showed antipsychotic effects of high-dose oral CBD with 60–69% improvement in scores on the Brief Psychiatric Rating Scale and Interactive Observation Scale for Psychiatric Inpatients after 4 weeks of CBD therapy (Zuardi et al., 1995). Preliminary results with CBD in additional schizophrenic patients are reported as promising (Gerth et al., 2002).

Anticonvulsant actions of CBD, comparable to those of diphenylhydantoin and other drugs that are clinically effective in major seizures, have been shown in a variety of animal models (Consroe and Snyder, 1986; Consroe and Sandyk, 1992). The effects are not reversed by CB1 antagonists, indicating that they are not CB1 receptor mediated. A small placebo-controlled clinical study of oral CBD as an add-on therapy in 15 patients with uncontrolled secondary generalized epilepsy with temporal focus was conducted by Cunha et al. (1980). Of the eight patients who received CBD over 4 months, four remained almost seizure-free and three others showed partial improvement, whereas the patients taking placebo showed no change.

Pharmacokinetic factors

When administered orally, the absorption of both THC and CBD is slow and erratic. Peak plasma concentrations are not reached for 2–6 h and the biological availability is 4–12% for THC (Grotenhermen, 2003) and 13–19% for CBD (Mechoulam et al., 2002). Both cannabinoids undergo extensive first pass metabolism in the liver and THC is also degraded by stomach acids. By contrast, inhaled cannabinoids reach peak plasma concentrations within minutes and have a bioavailability of approximately 35% for both THC and CBD. For medicinal purposes, other modes of administration have been investigated and sublingual liquid solutions appear to be well absorbed, producing rapid effects comparable to inhalation (Whittle et al., 2001; Grotenhermen, 2003; Wade et al., 2003). Using a sublingual spray of THC and CBD, Wade et al. (2003) found that it was possible for subjects with pain conditions or multiple sclerosis to self-titrate small doses that relieved pain and muscle spasms without inducing intoxication.

After absorption, both THC and CBD are sequestered in fatty tissues from which they are only slowly released (the tissue half-life is 5–7 days). Both cannabinoids form a large number of metabolites, which are gradually eliminated over days or weeks in the urine and faeces (Gold, 1992). There may be complex interactions between the two cannabinoids. CBD inhibits some cytochrome P450 enzymes and may inhibit the conversion of THC to its active 11-hydroxy metabolite (McPartland and Russo, 2001), but Zuardi et al. (1982) found no effect on THC levels in humans when the two cannabinoids were administered together. By contrast, THC and its metabolites, and even CBD on repeated administration, increase cytochrome P450 activity through enzyme induction (Grotenhermen, 2003).

Discussion

Despite the sparse anecdotal data in humans and the absence of controlled clinical trials, the evidence discussed above shows that both THC and CBD have pharmacological properties that could be therapeutic in patients with BAD. Furthermore, the available pharmacokinetic evidence indicates optimal methods of administration and dosage control. The underlying pathophysiology of BAD is unknown, but these cannabinoids, especially when used in combination, have several characteristics (Table 2) in common with drugs known to benefit this disorder, including antidepressants, antipsychotics, anticonvulsants (mood-stabilizers) and anxiolytics.

THC, in some conditions and doses, has anxiolytic, hypnotic and antidepressant effects with improvement in mood and general well-being in normal subjects, and in patients with pain conditions, multiple sclerosis or cancer (Regelson et al., 1976; Glass et al., 1980; Ashton et al., 1981; Fabre and McLendon, 1981; Ilaria et al., 1981; Paton and Pertwee, 1981; Martyn et al., 1995; Notcutt et al., 1997; Ashton, 1999b; Wade et al., 2003). These actions could be helpful in BAD, especially in depressive phases, which are often accompanied by anxiety (Goodwin and Sachs, 2004). CBD antagonizes the psychotic-like effects and intoxication liability produced by high doses of THC and has anxiolytic, hypnotic and anticonvulsant actions of its own in addition to a protective effect against glutamate toxicity (Cunha et al., 1980; Carlini and Cunha, 1981; Consroe and Snider, 1986; Guimaraes et al., 1990; Consroe and Sandyk, 1992; Zuardi et al., 1995; Zuardi and Guimaraes, 1997; Gerth et al., 2002; Mechoulam et al., 2002; Russo, 2003). These actions do not appear to be mediated by CB1 receptors but may result from enhancement of the endogenous anandamide system and effects on THC metabolism (Mechoulam et al., 2002; McPartland and Russo, 2001).

As well as adding to the anxiolytic effects of THC, the antipsychotic effects of CBD could be therapeutic in bipolar patients with psychotic symptoms, and the anticonvulsant and protective effects against glutamate toxicity may have a mood-stabilizing action similar to some other anticonvulsants of proven value in BAD (Porter et al., 1999; Ashton and

<table>
<thead>
<tr>
<th>Actions</th>
<th>THC</th>
<th>CBD</th>
</tr>
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<tbody>
<tr>
<td>Agonist action on CB1 receptors</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Inhibition of anandamide reuptake and hydrolysis</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Anxiolytic</td>
<td>+b</td>
<td>+</td>
</tr>
<tr>
<td>Psychotropic</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>−</td>
<td>+b</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>(+)</td>
<td>−</td>
</tr>
<tr>
<td>Sedative/hypnotic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antinociceptive</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuroprotective (inhibition of glutamate release)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Appetite stimulant</td>
<td>+</td>
<td>No data</td>
</tr>
<tr>
<td>Cardiovascular effects</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

aTHC is anxiolytic in some doses, but can be anxiogenic in higher doses or in drug-naïve individuals. bCBD also antagonizes some psychotic effects of THC. cShown in one study in cancer patients (Regelson et al., 1976). dTHC causes tachycardia and hypotension; CBD can cause bradycardia and hypotension.
various neurological disorders. Bipolar patients could self-titrate well tolerated and that side-effects were minimal in patients with drugs, necessitating dosage adjustment (Zullino Neurocognitive function, which is already impaired in BAD small dose preparations and a 50% CBD content in the medication. such a trial include the precipitation of hypomania, mania and psy-
regimes, duration of treatment, adverse effects and other factors.
scales, neuropsychological performance and a record of adverse 
clinical ratings of mania and depression scores, subjective rating 
contains 60–150 mg THC or more (Ashton, 1999b). Treatment 
obtainable daily would be 60 mg: a single modern cannabis ‘split’ 
and alcohol. Induction of cytochrome P450 enzymes may result in 
symptom control with the THC/CBD preparation may improve 
compromised by THC (Solowij, 1998). On the other hand, better 
interaction was attributed to slowed gut motility caused by 
when the patient stopped using marijuana (Ratey et al., 1981). The interaction was attributed to slowed gut motility caused by 
marijuana which increased lithium absorption.

Tolerance and dependence can result from chronic use of cannabis and withdrawal effects occur on ceasing use (Ashton, 1999a). However, little tolerance appears to develop to the putative therapeutic effects that have been studied. Some patients have found nabilone still to be effective for pain relief after 2–3 years of regular use (Notcutt et al., 1997) and patients taking plant-based cannabinoid extracts long-term for pain have not so far reported tolerance (Whittle et al., 2001). Any withdrawal problems could be minimized by tapering dosage if use was no longer required. Similar to cannabis, THC has abuse potential and precautions may be needed to limit patients’ overuse of the cannabinoid aerosols.

In conclusion, BAD is often poorly controlled by existing drugs and often involves a polypharmacological medley, including lithium, anticonvulsants, antidepressants, antipsychotics and benzodiazepines. Many patients take street drugs in addition, including cannabis, amphetamines, cocaine and illicitly obtained benzodiazepines in an attempt to control their symptoms. Some claim that such self-medication is superior to the drugs prescribed by psychiatrists. There are good pharmacological reasons for believing that the prescription of synthetic cannabinoids or standardized plant extracts may have a therapeutic potential in BAD. We suggest that the time is ripe for carefully managed trials of prescribed cannabinoids to determine whether they are of value as adjunctive drugs in bipolar patients whose symptoms are not adequately controlled by standard medications.

References


