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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 Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) may exert sedative, hypnotic, anxiolytic, antidepressant, antipsychotic and anticonvulsant effects. Pure synthetic cannabinoids, such as dronabinol and nabilone 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). Lamotrogine, although effective in biplar 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 Δ^9-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

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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

Electronic searches for relevant papers were performed, employing Medline (1966 to present), Embase (1980 to present), ISI Web of Science (1990 to present) and Psychoinfo (earliest available to present). Search terms were 'bipolar', 'manic depression', 'mania', 'antidepressant', 'antimanic', 'mood stabilizer', 'cannabinoid', tetrahydrocannabinol', 'THC', 'cannabidiol', 'CBD', 'cannabis, "marijuana", 'nabilone' and 'dronabinol'.

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 Δ^9-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 CB_1 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 CB_1 receptors that are present in the brain, spinal cord and peripheral nerves. CB_1 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.*,

Table 1 Localization of cannabinoid CB_1 receptors

Density	Localization	
Very dense	Basal ganglia	– globus pallidus, substantia nigra pars reticulata, entopeduncular nucleus
	Cerebellum	– molecular layers
	Hippocampus	– dentate gyrus
Dense	Cerebral cortex[a]	– layers I and VI
	Hippocampus	– CA pyramidal cells
	Corpus striatum	– caudate putamen
Moderate	Hypothalamus[a]	
	Basal amygdala[a]	
	Central grey substance	
	Nucleus of solitary tract	
	Spinal cord	
	Peripheral nerve terminals	
Sparse	Thalamus	
	Pons and Medulla	
	Some non-neural tissues, including spleen and testes	

[a]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).

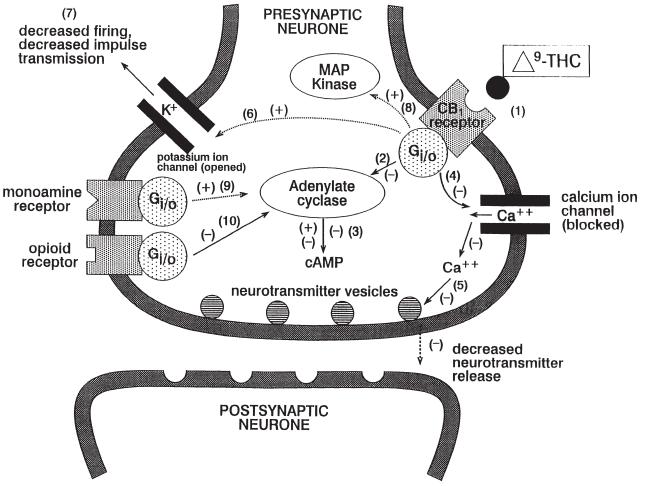

Figure 1 Schematic diagram of signal transduction mechanisms stimulated by CB_1 receptors. The CB_1 receptor (1) is coupled to a second messenger $G_{i/o}$ protein. Via this protein, activation of the receptor inhibits the enzyme adenylate cyclase (2) and decreases the production of cAMP (3). Via the G-protein, the inward flow of calcium ions is blocked (4), decreasing release of neurotransmitters (5). Also via the G-protein, the outward flow of potassium ions is enhanced (6), resulting in decreased neuronal firing and decreased impulse transmission (7). Stimulation of the G-protein also activates MAP kinase (8), affecting intracellular gene expression. Other receptors on the same neurone (for monoamines and/or opioids) may activate their own G-proteins but share a common adenylate cyclase, which they may stimulate (9) or inhibit (10). Anandamide is released in the post-synaptic membrane and acts retrogradely as an agonist on presynaptic CB_1 receptors (Howlett, 1995; Pertwee, 1997; Ameri, 1999; Joy *et al.*, 1999; Van der Stelt and di Marzo, 2003; Alger, 2004)

2003; Surguladze *et al.*, 2003). CB_1 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. CB_2 receptors are similar to CB_1 receptors but are present mainly in immune cells in the periphery and are not considered further here.

Activation of the CB_1 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). CB_1 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, CB_1 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 CB_1 receptors in the nervous system and CB_2 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-arachidonyl glycerol (2-AG). Anandamide is present in the brain in the same areas as CB_1 receptors. It is enzymatically synthesized in cell membranes, binds to CB_1 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 CB_1 receptors (Piomelli *et al.*, 2000; Christie and Vaughan, 2001; Wilson and Nicol, 2001; Van der Stelt and Di Marzo, 2003; Alger, 2004). By contrast, the exogenous cannabinoid THC is widely distributed, reaching all areas of CB_1 receptors, is very slowly eliminated (Agurell *et al.*, 1986) and produces effects lasting several hours (Maykutt, 1985).

CBD binds only minimally to CB_1 receptors and is usually described as non-psychoactive. However, the clinical observations described below suggest that it has antipsychotic, anxiolytic, anticonvulsant 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 glutamate toxicity, an action which is not affected by cannabinoid receptor antagonists (Mechoulam *et al.*, 2002). The possible contribution 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 modulate 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 neuromodulators, 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 administration, 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 moderate 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; Svendson *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 individuals, 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 psychosis with marked hypomanic features (Rottenburg *et al.*, 1982; Johns, 2001). In patients with BAD, the duration of cannabis use is associated positively with the duration of manic, but not depressive, 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 schizophrenia, 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 anticonvulsant 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.*, 1990). 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 predictive 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 CB_1 antagonists, indicating that they are not CB_1 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 sequestrated 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.

Table 2 Comparison of some effects of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD)

Actions	THC	CBD
Agonist action on CB_1 receptors	+	–
Inhibition of anandamide reuptake and hydrolysis	–	+
Anxiolytic	+[a]	+
Psychotropic	+	–
Antipsychotic	–	+[b]
Anticonvulsant	–	+
Antidepressant	(+)[c]	–
Sedative/hypnotic	+	+
Antinociceptive	+	+
Neuroprotective (inhibition of glutamate release)	+	+
Antiemetic	+	–
Appetite stimulant	+	No data
Cardiovascular effects[d]	+	+

[a]THC is anxiolytic in some doses, but can be anxiogenic in higher doses or in drug-naïve individuals. [b]CBD also antagonizes some psychotropic effects of THC. [c]Shown in one study in cancer patients (Regelson *et al.*, 1976). [d]THC causes tachycardia and hypotension; CBD can cause bradycardia and hypotension.

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 CB_1 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

Young, 2003). In addition, both THC and CBD have extremely low toxicity (British Medical Association, 1997; Mechoulam *et al.*, 2002).

Cannabinoids have already been tested for therapeutic effects in acute and chronic pain conditions and multiple sclerosis (Wade *et al.*, 2003; Svendsen *et al.*, 2004). The evidence suggests that a placebo-controlled trial of cannabinoids as adjunctive therapy in BAD should now be undertaken. Such a trial might start with a pilot investigation in treatment-resistant bipolar patients who remain symptomatic despite standard medications, choosing patients over the age of 18 years who have used cannabis previously (but who undertake to abstain from cannabis during the trial). Standardized plant extracts containing THC and CBD in combination and matching placebo have been available for clinical research since 1988 (GW Pharmaceuticals plc, Salisbury, UK). These could be self-administered as a 1 : 1 THC : CBD mixture or placebo and delivered by metered dose pump action aerosol spray as described by Wade *et al.* (2003). These authors found that the product was well tolerated and that side-effects were minimal in patients with various neurological disorders. Bipolar patients could self-titrate their preferred dosage to control symptoms and dosage would be minimized by limiting the amount contained in each spray to 2.5 mg of cannabinoid and the total dosage in each daily container to 120 mg cannabinoids. Thus, the maximum amount of THC obtainable daily would be 60 mg: a single modern cannabis 'spliff' contains 60–150 mg THC or more (Ashton, 1999b). Treatment periods would possibly be for 4 weeks, perhaps in a crossover active treatment/placebo design. Assessments would include clinical ratings of mania and depression scores, subjective rating scales, neuropsychological performance and a record of adverse effects. The results would provide information on optimal dosage regimes, duration of treatment, adverse effects and other factors.

Possible adverse effects that would require close monitoring in such a trial include the precipitation of hypomania, mania and psychosis, although these effects are unlikely to be significant with small dose preparations and a 50% CBD content in the medication. Neurocognitive function, which is already impaired in BAD (El-Badri *et al.*, 2001; Ferrier and Thompson, 2002) may be further compromised by THC (Solowij, 1998). On the other hand, better symptom control with the THC/CBD preparation may improve congnition. Additive effects may occur with hypnotics, sedatives and alcohol. Induction of cytochrome P450 enzymes may result in interactions with drugs metabolized by the same enzymes, including many antidepressants and antipsychotics. However, these enzymes are already induced in BAD patients who smoke tobacco or take cannabis. Two patients who stopped or reduced tobacco and/or cannabis consumption when on clozapine or olanzapine experienced adverse effects due to increased plasma levels of the drugs, necessitating dosage adjustment (Zullino *et al.*, 2002). A possible interaction between lithium and marijuana was reported in one case resulting in elevated serum lithium levels, which dropped 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.

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