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The Effect of Varenicline Administration on Cannabis and Tobacco Use in Cannabis and Nicotine Dependent Individuals – A Case-Series

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Abstract

Introduction: Cannabis users may also use tobacco products which increases the potential for drug-induced harm over and above that caused by one substance on its own. Therefore, a pharmacotherapy that treats dependence on both substances would be beneficial. Tetrahydrocannabinol and varenicline act at the α_7 subtype of the nicotinic receptor and so it was hypothesised that varenicline may also effect cannabis use.

Methods: Five nicotine and cannabis dependent individuals (median age 37), who were attending a community alcohol and drug service, and who expressed a desire to quit tobacco smoking, were prescribed 12 weeks of varenicline and were followed up weekly for the first month, then fortnightly for as long as possible over this time.

Results: Four of the five cases reported reducing their use of both substances after commencing varenicline, and also of experiencing less enjoyment from using these substances. The remaining case withdrew early in the study due to a migraine. No participant reported taking varenicline for more than 6 weeks, and only one could be followed up for 12 weeks. The reasons reported by participants for ceasing varenicline included feeling flat, experiencing nausea and vomiting, feeling angry and being short tempered, and as a result of a variety of family stressors.

Conclusion: The administration of varenicline to cannabis users was associated with reductions in the enjoyment reported from using cannabis, and the amount of cannabis used. These results support further investigation of varenicline's potential as a therapeutic intervention to treat dependence on nicotine and cannabis.

Keywords: Cannabis; Tobacco; Varenicline; Pharmacotherapy; Nicotinic Receptor; Case Series

Introduction

Cannabis is the most commonly used illicit drug of abuse in New Zealand (NZ); in 2008 15% of those aged 16-64 years of age reported having used it in the past 12 months [1]. Long term cannabis use can be associated with the development of dependence, which is manifest by a withdrawal syndrome on cessation [2,3]. During withdrawal, relapse to cannabis use is common as it relieves the symptoms of withdrawal [3]. The association between cannabis use and mental health problems (in particular anxiety, depression, and schizophrenia) and a number of other adverse life outcomes (such as poor educational outcomes and life satisfaction) has been reported [4-6]. Chronic use of cannabis also has adverse effects on pulmonary and cardiac health [3,7]. Survey evidence shows that frequent cannabis users (who do not smoke tobacco) are more likely to experience many of the respiratory problems that chronic tobacco smokers experience [8].

Many tobacco users also misuse cannabis, and *vice versa* [9,10]. While there are differences in the way people use both substances (some roll their own tobacco and cannabis 'cigarettes', others make 'joints' comprising of only cannabis), the concurrent use of cannabis and tobacco can add to the health burden experienced by such individuals, and may increase the potential for substance-induced harm over and above that caused by using one substance on its own [9,10]. Therefore, an intervention that can reduce the harm caused by both substances could be highly cost-effective, and would have immediate and long-term health benefits for individuals, irrespective of their age or current state of health.

Varenicline has demonstrated efficacy as a smoking cessation aid [11]. It is a partial agonist at the $\alpha_4\beta_2$ subtype of the nicotinic

acetylcholine receptor (nAChR) and a full agonist at the α_7 nAChR [12,13]. These receptors are found in the mesolimbic dopamine system region of the brain [12,14-16] and play a role in drug induced reward processes [15]. Varenicline is believed to facilitate tobacco smoking cessation through a dual mechanism. Firstly, it partially activates $\alpha_4\beta_2$ nAChRs located in the ventral tegmental area of the midbrain resulting in sufficient dopamine release in the nucleus accumbens to reduce nicotine withdrawal symptoms [12,14,17]. Secondly, via its antagonistic action, varenicline prevents full activation of the nAChR, hence reducing reward associated with smoking [12,14].

Tetrahydrocannabinol (THC) has also been shown to bind to α_7 nAChR [16]. Therefore, theoretically, it is possible that varenicline may also have an effect on cannabis use. In particular it would be expected to affect the enjoyment obtained from using cannabis, which in turn is likely to result in a reduction in the quantity of cannabis used. However, to date this hypothesis has not been explored. Currently no effective pharmacological treatment is available to treat cannabis withdrawal and dependence. Synthetic oral THC has been shown to

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be significantly more effective than placebo in reducing the severity of cannabis withdrawal [2,18]. However, it is unlikely to be made available to this client group due to concerns of misuse and diversion.

As it is biologically plausible that varenicline may have an effect on cannabis use, and in the absence of any published human data to support this hypothesis, the initial step needs to be a case study or case-series study. Indeed, such data are needed to support any further investigation. We undertook a prospective case-series to explore the relationship between the administration of varenicline and the reported enjoyment of using cannabis, and consequently the amount of cannabis used in nicotine dependent individuals who were also likely dependent on cannabis.

Material and Methods

Participants and procedure

Participants were outpatients attending the Community and Alcohol Drug Service (CADS) in Auckland, NZ and met the following inclusion criteria: aged ≥ 18 years; willing to provide written consent; not pregnant/breast feeding; used both tobacco and cannabis (not together to avoid the confounding effects of a reduced desire to use one but not the other substance); reported that their first tobacco cigarette was within 30 minutes of awakening and were motivated to quit smoking tobacco; scored ≥ 12 on the Cannabis Use Disorder Test-Revised (CUDIT-R) which is indicative of a cannabis disorder [19]; had no contraindications to the use of varenicline and met the NZ criteria to receive government subsidised supply of varenicline (i.e., tried to quit smoking tobacco using NRT patches on two occasions and failed, or tried to quit smoking using bupropion or nortriptyline and failed). Ethical approval to undertake this study was obtained from the New Zealand Northern Regional Ethics Committee (NTX/11/11/100)

Flyers advertising the project were posted throughout CADS. Interested individuals contacted a researcher by phone who in turn conducted a preliminary screen to ensure they met eligibility criteria. Those eligible were medically assessed to confirm that they met eligibility criteria and to obtain written consent. They were provided with a prescription for a 12 week course of varenicline (standard dose of 0.5 mg once a day for the first three days of treatment, then increased to 1 mg once a daily [20], and were referred to a research assistant for a baseline assessment. Participants were asked not to commence varenicline prior to attending the baseline assessment. At this assessment participants set a tobacco quit date (usually one week after they started varenicline), and then were followed up once each week for the first month and then fortnightly thereafter, until the course of varenicline was completed. All attempts were made to follow-up participants for the full 12 weeks even if they did not complete the course of varenicline.

Participants were encouraged to report any history of psychiatric illness, and cardiovascular illness at the time of screening. A researcher was on call at all times during the study and participants were encouraged to contact this person if they experienced any symptoms that concerned them, in particular, any changes in behaviour and thinking, anxiety, psychosis, mood swings, agitation, aggression, depressed mood, suicidal ideation and suicidal behaviour. Participants were given supermarket vouchers to the value of NZ\$10 for attending each clinic visit.

Measures

At baseline, demographic information on participants' tobacco and cannabis use history, and attempts at quitting of both substances were

collected. In addition the following were administered: the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) which provides information on life and current (past three months) alcohol and drug use and produces a score for each drug that can be used to classify people into either a low (scores 0-10 for alcohol, 0-3 for other drugs), moderate (11-26 for alcohol and 4-26 for other drugs) or high risk (27+) category [21]; the Severity of Dependence Scale (SDS) which assesses the degree to which the individual met a number of criteria reflecting psychological dependence on cannabis [22] - a score of ≥ 4 on the SDS is indicative of psychological dependence on cannabis [23]; and the first two questions of the Fagerstrom Test for Nicotine Dependence (FTND) [24]. They were also asked to rate their chances of giving up either tobacco or cannabis on a scale 1 (very low) to 5 (very high).

At each subsequent assessment participants were administered the SDS, were asked about the amount and types of cannabis and tobacco used, and how enjoyable they found cannabis since their last assessment using a five level Likert scale (much less, slightly less, same as usual, slightly more, much more), were asked to rate their chances of giving up either tobacco or cannabis, the existence of a number of adverse events and, were asked if they took the varenicline as prescribed.

Results

Fourteen clients volunteered for this study and were screened for eligibility. Six were judged ineligible on the basis of the following; three reported not using cannabis or scoring < 12 on the CUDIT-R; two reported not using tobacco; and one had severe past and current psychiatric problems. In addition, three clients could not be contacted following the preliminary screen. Therefore, five clients are included in this case series. All were enrolled with the Methadone Service at CADS. They were three males and two females with a median age of 37 years (range 31-49 years). One participant (male) self-identified as NZ Māori, the remaining as NZ European. At baseline all participants reported frequent use of tobacco and cannabis (at least four times a week). The baseline CUDIT-R scores ranged from 16 to 25 which suggests that all participants would likely have met criteria for a cannabis use disorder at that time [19]. Furthermore baseline SDS scores for cannabis ranged from three to nine, with two participants scoring above four (five and nine, respectively) which is indicative of psychological dependence on cannabis [23]. The duration of the most recent uninterrupted cannabis use ranged from two to 27 years, as did tobacco use. Only one participant expressed a desire to quit cannabis at baseline rating his chance of succeeding as moderate (2.5 on a scale of 5); he also rated his chance of giving up tobacco as very high (score of 5). Four participants reported drug use other than tobacco and cannabis. Two scored 'very high' for alcohol (ASSIST score > 30), two scored 'moderately high' for opioids (ASSIST scores 8 and 20), and one client scoring 'very high' for use of amphetamine-type stimulants (ASSIST score 30) (Table 1).

Outcomes for the five participants are summarised in (Table 1). The participants self-reported taking varenicline from two to six weeks, and all, except for one who was followed up for the full 12 weeks, were lost to follow up soon after they ceased taking varenicline. Two participants reported that nausea complicated initiation onto varenicline, and that this resulted in erratic compliance with the dosing schedule thereafter. The remaining participants reported that they complied with the dosing schedule before they stopped taking varenicline. The reasons given by participants for stopping varenicline included headache (n=1), nausea and vomiting (n=2), family stressors (n=2), anger/short temper (n=2), and feeling flat (n=1).

#	Age	Sex	Baseline drug use		Duration of recent continuous use (yrs)		Baseline cann SDS ³	Want to quit cann	Self-reports : quantities of substance used/ enjoyment of using while taking varenicline	Reasons stopped Tx	Notes (drug use outcomes following treatment; duration of varenicline treatment; duration of follow up)
			¹ CUDIT score	² ASSIST score	Tob	Cann					
1	49	F	17	Tob=15 Cann= 9 Al=3 Op= 6	27	10	3	No	Enjoyed tobacco less, but used the same amount. No effect on the enjoyment or amount of cannabis used.	Migraine headache and vomiting	Erratic compliance due to bouts of nausea which forced the client to delay setting her quit date many times. Her general practitioner prescribed anti-nausea medication, but this did little to help. No change in SDS scores. Lost to follow up after 6 weeks in study. (2 weeks ^a ; 6 weeks ^b)
2	31	M	16	Tob=26 Cann=12 Al=31	16	13	5	Yes Rating (2.5/5)	Reduction in the amounts of tobacco and cannabis used (reported nil use at second follow-up, i.e. 2 weeks). Reduction in the enjoyment of using both drugs.	Feeling flat	Reported taking varenicline for 4 weeks as prescribed. SDS dropped to zero soon after starting varenicline, but returned to baseline level once ceased. Following the cessation of varenicline the amount of tobacco and cannabis used returned to similar levels as baseline, but the client continued to report less enjoyment from using both substances (4 weeks ^a ; 12 weeks ^b)
3	39	F	19	Tob=24 Cann=15	3	23	3	No	Reported reduction in the enjoyment obtained from using both substances, but no change in the amounts used.	Family stressors	Reported taking varenicline for 5 weeks. SDS dropped to zero during this time. The client reported that the reduction in the enjoyment obtained from using both tobacco and cannabis persisted even after ceasing varenicline. Lost to follow up 2 weeks after ceasing varenicline (5 weeks ^a ; 7 weeks ^b)
4	37	M	25	Tob=24 Cann=15 Al=3 ATS=3 Op= 8	3	29	9	No	Reported a reduction in the amounts used and the enjoyment from using both substances.	Nausea and vomiting/ family stressors	Reported taking varenicline for 6 weeks and missing a few doses due to nausea and vomiting. The reduction in the amount and the enjoyment obtained from using both substances persisted after the client stopped taking varenicline. SDS dropped to 1 (from 9) soon after starting varenicline and remained at this level at each subsequent assessment point. Lost to follow-up the week after the client ceased taking varenicline. (6 weeks ^a ; 7 weeks ^b)
5	35	M	16	Tob=21 Cann=19 Al=32 ATS=30 Op= 20	2	2	3	No	Reported a slight reduction in the amounts used and the enjoyment from using both substances	Anger and short temper	Nausea complicated initiation onto varenicline. Erratic compliance thereafter. Attributed anger/short temper to varenicline or stopping smoking – resumed smoking tobacco Lost to follow-up 4 weeks into study (2 weeks ^a ; 4 weeks ^b)

Notes: ¹CUDIT = Cannabis Use Disorders Involvement Test – Revised. Score of ≥12 indicative of problematic cannabis use disorder [19]; ²ASSIST= Alcohol, Smoking and Substance Involvement Screening Test [21]. Scores are for current (3 month) drug use. Scores are indicative of low risk (0-10 for alcohol and 0-3 for other drugs), moderate risk (11-26 alcohol; 4-26 other drugs) or high risk (27+ all drugs); ³SDS=Substance Dependence Scale [22, 23]; Tob = Tobacco; Cann = Cannabis; AL = Alcohol; ATS=Amphetamine-type stimulants; Op=opioids; Tx = treatment; ^aself-reported time taking varenicline. ^bduration of study followed up

Table 1: Summary of Cases.

All participants reported a reduction in the enjoyment of using tobacco during the time they were taking varenicline and four reported a reduction in the amount of tobacco they had used during this time. Four participants reported a reduction in the enjoyment obtained from cannabis, and also the amount of cannabis used during the time they were taking varenicline. Indeed, one participant (Case 2) reported that they had not used either substance over a two week period whilst taking varenicline. One participant (who reported erratic compliance due to bouts of nausea and vomiting) reported no change in the enjoyment they obtained from using cannabis, or the amounts they used. The finding that the SDS score for cannabis dependence reduced to zero in two cases (from 5 and 3, respectively) and from nine to one in another, is consistent with the reports of reduced desire to use cannabis. In three cases the reduction in either, the enjoyment experienced from using cannabis, and/or the amount of cannabis used, persisted for some time after participants stopped taking varenicline.

Discussion

The objective of this case series was to explore the link between the

administration of varenicline and the reported enjoyment from using cannabis and, in turn, the quantity of cannabis used, in those dependent on nicotine and likely dependent on cannabis. Participants' self-reports with respect to these outcomes were encouraging. Four of the five participants self-reported a reduction in the enjoyment obtained from using cannabis, and three of the latter group also reported a reduction in the amount of cannabis used whilst taking varenicline.

Pivotal to the discussion concerning the reduction in the enjoyment of cannabis is whether this was related to the consumption of varenicline. While it is, of course, not possible to infer causation on the basis of these findings, in all cases where there were reported changes there was a clear temporal association between the continued use of varenicline and the reported reduction in desire and enjoyment of cannabis. Indeed, in a number of cases the reduction in either the enjoyment experienced from using cannabis, and/or the amount of cannabis used, persisted for some time after participants stopped taking varenicline.

To be eligible for this study participant were required to want to

quit smoking tobacco, but not cannabis, and so there was no external pressure to alter their use of the latter. Furthermore, all participants were enrolled in the Auckland Methadone Service and attended CADS for regular outpatient treatment, but did not report receiving any current treatment for tobacco or cannabis use. Cannabis use is common among methadone maintained patients [25], but has been found to have no measurable effect on treatment outcomes [26]. Scavone and colleagues [27] reported that while cannabis use was relatively high during induction onto methadone, it dropped significantly following stabilisation. Participants in this study were not undergoing methadone induction and so therefore it is unlikely that the reported reductions in cannabis use could be attributed to the effect of methadone treatment.

The finding that all participants stopped taking varenicline prior to completion of the 12 week course of the treatment is disappointing. Participants reported a variety of side effects whilst taking varenicline. Headache and vomiting, feeling flat, feeling nauseated and vomiting, and feelings of anger and being short tempered were attributed to taking the drug by four participants. None of these reports of adverse effects is surprising. Data from clinical trials show that gastrointestinal symptoms (commonly nausea) and fatigue were amongst the most common side effects reported (occurring at the rate of $\geq 1\%$, and incidence higher than placebo) [20]. More recently, varenicline has been implicated in violence towards others, which may manifest as anger [28], but there are few other reports of this effect.

Conclusion

Findings from these cases suggest a link between the administration of varenicline and a reduction in the enjoyment experienced from using cannabis and reduction in the amount of cannabis used. We postulate that the probable mechanism responsible for this effect is the action of varenicline at the α_7 nAChR, which is a common receptor target for both varenicline and THC. Indeed the α_7 nAChR has been implicated, through *in vivo* animal studies, as a possible target for pharmacological agents to treat cannabis abuse [17]. As far as the authors are aware, these results are the first to demonstrate this phenomenon in humans, but there is a need for larger controlled studies to more definitively demonstrate this phenomenon. These future studies will also need to monitor the incidence of side effects, in particular nausea that might affect induction onto varenicline and ultimately success of using this drug for this purpose. Furthermore, alcohol is also known to target nAChRs [29]. Recent early human trials have shown that varenicline reduces alcohol craving, and the rewarding effects and quantity of alcohol consumed [30-32], and therefore alcohol consumption should also be monitored.

Given that many tobacco smokers also smoke cannabis [9,10] we argue that the availability of a therapeutic intervention, such as varenicline, that has the potential to target the misuse of both substances would confer significant health benefits for these individuals.

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