Editorial

Coming off prescribed psychotropic medications: insights from their use as recreational drugs

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Short Title: psychotropics as recreational drugs

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Introduction

Cosci and Chouinard (1) present a very elegant and thought-provoking overview. They comment extensively on the potential possessed by a range of therapeutically prescribed, under appropriate medical control, psychotropics of being associated with a short-/long-term withdrawal syndrome when discontinued. This is a relevant clinical topic; indeed, in parallel with a decline in the UK of both benzodiazepines (BDZ) and Z-drugs (e.g. zaleplon; zolpidem; zopiclone), a significant increase in antidepressants'; second generation antipsychotics'; and gabapentinoids' prescriptions have been observed (2; 3).

Recreational and prescribing psychotropics; terminology issues

Recreational, abused drugs (e.g. cannabinoids; cocaine; MDMA/ecstasy) appear to increase dopaminergic signalling in ventral striatal regions, including the nucleus accumbens, a key site of the mesolimbic reward pathway (4; 5). Increased activity in striatal dopaminergic signalling pathways is likely associated with their subjective rewarding, euphoric and reinforcing effects of such molecules. Conversely, reduced dopaminergic transmission in the limbic system plays a role in drug craving; withdrawal; and relapse into compulsive drug intake (5).

Furthermore, recreational drugs are considered to possess no, or very limited, therapeutic value.
When referring to *therapeutically prescribed* molecules, however, there are levels of clinical terminology confusion (6). In fact, the related terms 'misuse'; 'abuse'; 'dependence'; and 'addiction' are often used in the literature without standardized definitions. From a pharmacovigilance (7) perspective, '*misuse*' is the intentional and inappropriate use of a product other than as prescribed or not in accordance with the authorized product information, whilst '*abuse*' is the intentional non-therapeutic use of a product for a perceived reward, including 'getting high'/euphoria (8). Conversely, *dependence* is characterized 'per se' by tolerance and/or withdrawal symptoms (9), with '*withdrawal*' however not necessarily including the occurrence of *physical* signs and symptoms (10). Finally, '*addiction*' is characterized by a further range of issues, e.g. compulsive substance use; cravings; and continued use despite its adverse consequences (6; 11-12). Hence, withdrawal symptoms that occur upon discontinuation of medications prescribed for valid medical reasons do not suggest, per se, either a substance-related (13) or an addiction disorder (6). This may well be the case with both antidepressants (ADs; 14-16) and benzodiazepines (BDZ; 17).
Withdrawal, a more appropriate term than 'discontinuation' (18), syndromes occur with most recreational, and a range of prescribed, drugs (15). These syndromes may include the following features: a) rebound, e.g. the re-occurrence of the original symptoms for which the index medication was prescribed; b) withdrawal, including both rebound and new, unrelated, symptoms; and c) persistent post-withdrawal disorder, characterized by a return of higher severity original illness, often associated with additional features (1).
Withdrawal syndromes have been interpreted in light of the concept of behavioural toxicity (1, 19-21). In 1968, Di Mascio and Shader (22) specifically addressed the behavioural toxicity of psychotropics. They referred to the pharmacological actions of a drug that, within the dose range in which it has been found to possess clinical utility, may produce a range of psychological and behavioural alterations, thus limiting the capacity of the individual or constituting a hazard to his/her well-being. Such a concept was revisited by Fava et al. (21) in 2016. It may thus be of interest to analyze these phenomena in a population where psychotropic drugs are clearly misused/abused to outline similarities and differences.

High-dosage medications' misuse/abuse; the psychonauts' world
In clinical psychiatry settings, the therapeutically prescribed medicines' intentional misuse and abuse may well be an unusual observation. It is here argued, however, that these same prescribing molecules, when ingested by those with a substance abuse history; at largely supra-therapeutic dosages (e.g. pregabalin; venlafaxine; quetiapine); and/or with modalities that increase their bioavailability (e.g. loperamide) may

be associated with a clear cut 'reward' sensation. This is at odds with other reports, suggesting that medications' misuse may be associated with only soothing effects, but little else (6).
Indeed, a range of prescribed medications are currently being used recreationally, typically at high-/super-high dosages, as new/novel psychoactive substances (NPS; 23). Within both online drug forum communities and social networks, there are some educated/informed users (the 'psychonauts'; 24) who are keen to 'test' a range of molecules, including prescribing psychotropics, to achieve specific mindsets. Their information is routinely being shared online (24) and vulnerable subjects, including both children/adolescents and psychiatric patients, may hence be at-risk of accessing these 'pro drug' data (25).
Psychonauts are a clinical 'niche', and their idiosyncratic levels of medications' intake are better scrutinized with the help of the netnographic research approach (26). This approach should be interpreted as a 'magnifying lens', aimed at shedding further light on the putative misuse; abuse; and dependence potential of those psychotropics being prescribed by practicing psychiatrists.
The focus will be here on the different withdrawal; misuse; abuse; and dependence issues associated with the typically high-/very high-dosage recreational intake of a range of prescribed psychotropics, including: GABAergics; antidepressants; ketamine and related drugs; antipsychotics; gabapentinoids; and over-the-counter opiates/opioids.

GABAergics (benzodiazepines; 'Z-drugs'; GABA-A/GABA-B agonists)

Prescribed and designer/'exotic' benzodiazepines
According to a recent EU-wide emergency department-admissions' survey, the most frequently misused benzodiazepines were respectively clonazepam, diazepam, and alprazolam (27). In parallel with this, a range of NPS belonging to the BDZ class have recently appeared on the street/online/virtual markets and are known as '*legal/exotic/designer'* benzodiazepines. Exotic BDZ were either tested, but not approved, as medicinal compounds or are derivatives of currently prescribed BDZ. For most of them, only very little pharmacology and toxicity knowledge is available (26). Most typically, online BDZ purchasers are per definition not aware if they are taking traditional; designer; or counterfeit BDZ.
Although there are a few hundreds of exotic BDZ discussed within the NPS community (28), a non-participant, multilingual, qualitative/netnographic study recently focused on those 29 exotic BDZ which have been formally identified as NPS by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (26). They can be ingested, snorted or injected (29; for an overview of related clinical features, see Table 1).

Z drugs

Although sharing with benzodiazepines a similar mechanism of action, Z-drugs appeared on the market as safe substitutes for benzodiazepines, purportedly having both a reduced abuse potential and propensity to induce less tolerance and withdrawal due to improved pharmacokinetics (30). Z-drugs' withdrawal symptoms are similar to those observed with BDZ (see Table 1; 31). However, their idiosyncratic routes of administration and the high-dosage intake may well increase the risk of Z-drugs' withdrawal issues (32).
Schifano et al (33) analysed the Adverse Drug Reactions (ADR) datasets provided by the European Medicines Agency (EMA) through the EudraVigilance (EV) system. An overall total of 33,240 (e.g. 23,420 zolpidem; 9,283 zopiclone; and 537 zaleplon) misuse/abuse/dependence and withdrawal-related ADRs, corresponding to some 6,246 unique patients, were identified. Out of these three molecules, zolpidem and zopiclone presented with the same dependence risk, but zolpidem was the most frequently associated with withdrawal issues. Zaleplon was the least reported for these ADRs (see Table 1).

GHB/GBL
Currently used in some countries to treat narcolepsy and alcohol withdrawal, gamma-hydroxybutyric acid (GHB; 'liquid Ecstasy') intake is associated with both increased central Dopamine levels and activation of GABA-A/B receptors (34). The GHB withdrawal syndrome has been well characterized (Table 1). In the UK, Corkery et al (34) described 159 GHB/GBL-associated fatalities; most (79%) were accidental and GHB/GBL alone was implicated in 37% of cases.

Phenibut
Phenibut/'PB' is openly available online as both a nootropic and a dietary supplement. When misused at high dosages (Table 1) it acts as an GABA-A/B receptors' agonist, whilst stimulating Dopamine/Serotonin neurotransmission as well. Its use may rapidly lead to dependence; withdrawal signs/symptoms may include visual and auditory hallucinations (29; Table 1)

Baclofen
Baclofen is a GABA-B agonist showing both anxiolytic and analgesic properties; the intake of high dosages is associated with euphoria, relaxation and anxiety blocking effects. Baclofen should always be withdrawn gradually (29; Table 1).

Antidepressants (ADs)
Out of all ADs, bupropion and venlafaxine have emerged as increasingly being misused and abused (35). Both high/very high (e.g. up to 4,050 mg/day, roughly 14 times higher than the maximal therapeutic dosage with oral, nasal, and intravenous use) bupropion's stimulant effects have been reported (Table 1), consistent with its action both as a selective

inhibitor of Noradrenaline/NA and Dopamine/DA reuptake. Bupropion is a cathinone derivative, resembling the remaining large number of synthetic cathinones' NPS (36). Typical bupropion idiosyncratic dosage abusers may present with a history of drug addiction and/or are inmates (35; 37; Table 1). Even venlafaxine, at mega dosages, can be misused and abused (38; Table 1); this is consistent with desvenlafaxine, being an inhibitor of NA transporter activities, further increasing the rate of DA turnover in the prefrontal cortex (39). In line with these observations, both the last decade European Medicines Agency (EMA) and the UK-based Yellow Card Scheme pharmacovigilance adverse drug reactions (ADRs) data (40) showed that, in comparison with venlafaxine, bupropion may possess a higher stimulant-like recreational activity. Conversely, the occurrence of a withdrawal syndrome was confirmed to be a significant issue for venlafaxine-treated patients (40).

Ketamine and related drugs

Ketamine psychiatric prescribing is on the increase (41); and the UK National Institute of Clinical Excellence (NICE) is currently reviewing the possibility of its derivative esketamine being used for treatment-resistant depression. However, because of ketamine-related compounds' associated psychosis and misuse, this decision has sparked levels of controversy (42). Ketamine acts as an N-methyl-D-aspartate (NMDA) receptor antagonist, whilst inhibiting both the voltage-gated Na/K channels; Serotonin; and DA reuptake. All these actions are likely contributing to both its significant psychoactive effects and addictive liability issues (43-44; Table 1). The occurrence of ketamine-associated urinary dysfunction's (45) painful symptoms can facilitate persistence in ketamine intake, because of its analgesic properties. There are a range of ketamine/'special K'-related molecules being widely misused by psychonauts, including methoxetamine ('special M'; 46) and dextromethorphan (DXM; 'green triangle), an over-the-counter cough/cold remedy (29).

Antipsychotics (quetiapine; olanzapine; clozapine)

Commonly prescribed in the 400–800 mg/day range, quetiapine ('Susie Q'; 'Q ball' and 'Maq ball' if respectively associated with cocaine and marijuana) appears to be the most documented antipsychotic being abused either on its own, or in combination (17). Its extended-release (XR) formulation may be less frequently misused and abused, due to the delayed (by approximately 3 h) and blunted (by approximately 67%) serum peak; the tablet coating may also make snorting of the crushed tablets quite problematic (47). Prison inmates and opioid addicts seem to represent the most at-risk populations. Quetiapine psychotropic effects are associated with both increased levels of DA in the nucleus accumbens (NAc) area (48) and D2 receptor blockade, although norquetiapine-related NA reuptake blockade; 5-HT7 antagonist properties; and sigma receptor activation; may contribute to its misuse liability (for a review, see 16).

Conversely, olanzapine high-dosage has been anecdotally reported as the 'ideal trip terminator/modulator' (49-50). These misusing liability levels may be associated with: olanzapine-related activity on GABA-A receptors, hence the associated sedation; the rewarding glutamatergic stimulation of the ventral tegmental area DAergic neurons; the 5HT2C and histamine/H1 antagonist properties; and the potent inhibiting action on the muscarinic M1 receptors (for a review, see 35).
All voluntary European Medicines Agency database reports relating to both quetiapine (2005-2016) and olanzapine (2004-2016) were recently analysed (34). From the EMA database, 18,112 (8.64% of 209,571) and 4,178 (7.58% of 55,100) ADR reports of misuse/abuse/dependence and withdrawal were associated with quetiapine and olanzapine, respectively. The resulting proportional reporting ratio (PRR) values suggested that the withdrawal-related ADRs were more frequently reported for quetiapine, with a PRR=5.25, in comparison with olanzapine (51).
Although clozapine is known to present with a range of well-known side-effects, only anecdotal description is available relating to its putative withdrawal syndrome. Chiappini et al (52) recently analysed the 2005-2018 EMA dataset of ADRs to identify and describe possible clozapine withdrawal-related issues. Out of 11,847 clozapine-related ADRs, some 258 were withdrawal-related (52).

Gabapentinoids

Following initial reports from this Journal (53) the gabapentinoids pregabalin and gabapentin have been clearly identified as possessing a distinct potential for misuse (54). Chiappini and Schifano (55) aimed at assessing cases of gabapentinoid misuse or dependence as reported to the EMA EV database. All voluntary reports of both gabapentin-(2004–2015) and pregabalin- (2006–2015) were retrieved. Some 7,639 (6.6 % of a total of 115,616) and 4,301 (4.8% of 90,166) ADR reports of misuse/abuse/dependence were, respectively, associated with pregabalin and gabapentin. Misuse/abuse/dependence-related entries were more frequently reported for pregabalin compared with gabapentin; frequent levels of co-ingestion with opiates/opioids was identified, especially in fatalities.
Overall, gabapentinoids may induce a 'liking' (euphoric high) subjective feeling, but more limited levels of 'wanting'/behavioural dependence (for an overview, see 56). Indeed, patients may report pleasant stimulation and euphoria only when using supratherapeutic/mega (e.g. 1,500-12,000 mg) pregabalin dosages (56). Hence, one could wonder if there may be a different/unclear range of neurotransmitter involvement, and receptors' activation intensity, in mega levels of pregabalin dosage ingestion (Table 1).

Opiates/opioids; loperamide

A massive, recent, worldwide increase in opiate/opioid prescription levels has been identified, with fentanyl being a reason of particular concern (57-59). Within the OTC abuse ('pharming') opiate/opioid scenario, the antidiarrhoeal loperamide has increasingly been reported by psychonauts as a recreational drug (60). Loperamide acts as a potent mu-opioid receptor agonist, albeit with predominantly peripheral activity on the myenteric plexus. Loperamide high-dosage ingestion has been associated with euphoria (60); different techniques are being used to increase its low bioavailability levels (35; 60; see Table 1).

Conclusions

The current editorial has taken inspiration from the thought-provoking Cosci and Chouinard (1) paper; they focussed on the withdrawal syndromes associated with a range of therapeutic dosage, medically prescribed, psychotropics' intake. The issues associated with these same psychotropics, albeit ingested as advised by the psychonauts, have been described here.

It is here suggested that when selected psychotropic medications are self-administered at mega-, as opposed to therapeutic, dosage levels, the associated *withdrawal; persistent post-withdrawal*; and overall *behavioural toxicity* issues may be particularly relevant. Indeed, when tapering down a therapeutic dosage AD, symptoms most typically are both mild/go untreated; and resolve spontaneously (21). However, when high-/mega-dosage ADs (37; 61); gabapentinoids (62); or BDZ (26) are discontinued, the intense related *withdrawal* symptoms *will always* need proper, long-term, specialist attention. Second, the occurrence of a *persistent post-withdrawal disorder* is *only occasionally* observed with both antipsychotics (e.g. tardive dyskinesia and supersensitivity psychosis) and ADs (e.g. mood fluctuations; 16). Conversely, with high-dosage medications (e.g. negative affect; dysphoria; and protracted insomnia for opiates/opioids; 63) is *very frequently* reported. Finally, the range of psychotropics' intake-related *behavioural toxicity* syndromes which at therapeutic dosage are *at times* observed may include: alterations in mood, perceptual, cognitive and psychomotor functions (21), but also both 'paradoxical' (e.g. increased anxiety and rage, as opposed to sedation, with benzodiazepines) and 'pendular' drug effects (e.g. excessive/euphoric mood lifting modifications with ADs) (22). Conversely, at mega psychotropics' dosages the range of the above clinical effects are being *typically* observed, indeed representing the sought-after effects. This is especially true for: venlafaxine (MDMA-like perceptual disturbances); bupropion (excessive mood lifting, pendular drug alterations; 64); pregabalin (perceptual disturbances/dissociative effects); and quetiapine (intense psychomotor function retardation effects). Further, the therapeutic dosage benzodiazepines' intake may be associated with paradoxical effects only in selected, e.g. personality disorder (65) or elderly (66), patients', subgroups. Conversely, the high-

dosage; highly potent; BDZ/novel BDZ are often ingested to achieve proper stimulant/aggressive, as opposed to sedative, effects (65; 67) Increasing levels of access to the web over the past 15 years or so may have contributed to the current scenario of prescribed drugs' misuse and abuse, with social networks having played a role in prescription drugs' aggressive marketing/distribution from rogue websites (25). However, one should here emphasize that, for most prescription molecules here discussed, including gabapentinoids, pre-marketing processes were not able to appropriately identify their misuse and abuse potential. Pre-authorization trials however typically involve the administration of carefully controlled, daily limited, therapeutic dosages and subjects with a current/previous history of drug misuse are excluded (68). Hence, the molecule's possible potential for abuse will be fully appreciated only when the real-world client population, involving vulnerable individuals, is exposed to it. Because of a likely post-marketing reporting bias (e.g. clinicians typically flagging only those molecules which have already been identified as at-risk for misuse and abuse), pharmacovigilance should identify a range of technical tools and approaches to go beyond voluntary reporting systems.
At high-/very high- dosage, a range of medications including antidepressants, antipsychotics, and gabapentinoids can be self-administered as proper drugs of abuse. Physicians should be vigilant when prescribing drugs with an abuse/misuse/diversion potential (69) and carefully evaluate the risk for some clients to be prone to ingest high-/mega-dosage medications, often in combination with alcohol and illicit drugs. Prescribers should hence be aware of the possibility of feigning psychiatric symptoms in order to obtain specific medications (70).

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Table 1: Acute intoxication; withdrawal; and clinical issues associated with a range of high-dosage, prescribing psychotropics', intake

Drug category	**Typical acute intoxication signs/symptoms**	**Typical withdrawal's clinical features**	**Examples of recreational high-dosage levels ingested; information about drug's potency**
GABAergics; *Most popular traditional benzodiazepines (BDZ)* Alprazolam; clonazepam; diazepam (27) *Typical 'exotic/designer' benzodiazepines (BDZ)* Phenazepam, etizolam; pyrazolam; flubromazepam; diclazepam; meclonazepam; deschloroetizolam; flubromazolam; nifoxipam; clonazolam/clonitrazolam; adinazolam; nitrazolam; metizolam; clonitrazolam; 3-hydroxyphenazepam; fonazepam; 4-chlorodiazepam; flunitrazolam; bromazolam; norfludiazepam, Ro-07-4065, thionordiazepam; methyl-clonazepam; fluclotizolam; tofisopam; flualprazolam; clobromazolam/phenazolam; bentazepam (26)	For phenazepam, the most well-known exotic molecule: it can be ingested, snorted or injected; euphoric effects but also amnesia, drowsiness, dizziness, somnolence, difficulty in waking up, muscle weakness, headache, weakening of attention, incoordination, blurred vision, slurred speech, ataxia, and muscle weakness. At high dosages, delirium and psychosis-like behaviour (26; 29 27)	Similar to traditional BDZ, withdrawal, dependence and tolerance have been documented. The withdrawal syndrome may however be arguably more intense when abruptly discontinuing potent/very potent BDZ	Alprazolam: 30 mg or even higher dosages being anecdotally reported Clonazepam ingestion: oral; snorting; intramuscular. Dosage: euphoria being achieved with 8-12 mg (53) Phenazepam is 5-10x more potent than diazepam (26; 29) Etizolam: being ingested at > 4 mg (26) Pyrazolam is 12x more potent than diazepam; dosage: > 3-4 mg (26) Flubromazepam: >8-12 mg (26) Meclonazepam: >1-2 mg (26) Flubromazolam: 400-600 μg is considered a very high dosage (24)
Z drugs (zaleplon, zolpidem, and zopiclone)	Among Z-drugs, zolpidem is the most frequently misused and zaleplon the least; concomitant use of recreational drugs possible (33)	Withdrawal signs/symptoms may include: insomnia, anxiety euphoria irritability, tremor, inner restlessness, speech difficulties, abdominal pain, hypertension, tonic-clonic seizures, and confusion/disorientation/delirium (31)	Oral; nasal insufflation; intravenous intake reported (33)
GHB/GBL	Euphoria and calmness are initially observed after ingestion. High dosages lead to drowsiness, nausea, vomiting, muscle stiffness, dizziness, confusion, delirium, hallucinations, convulsions and cardiopulmonary depression. Fatalities described (34).	GHB is highly addictive; withdrawal syndrome: insomnia, muscular cramping, tremor and anxiety (29; 34)	GHB elimination half-life is 27 minutes, hence the re-dosing risk; 10 mg/kg (0.75 g) is considered only a low/moderate recreational oral dose (29)
Phenibut	May rapidly lead to dependence/tolerance. Acute	Withdrawal signs/symptoms may include: visual and auditory	Taken orally in dosages (e.g., 1-

	intoxication is characterized by tachycardia, visual hallucinations, tremor, nausea and vomiting; serotonin syndrome possible (29)	hallucinations, psychomotor agitation, derealization, depersonalization, increased light and sound sensitivity, muscle pain/twitches, tachycardia, nausea, tremor and insomnia (29)	3 g) notably superior to the therapeutic ones (29)
Baclofen	Euphoria, relaxation and mood-lifting effects; resembling a high-dosage GHB and/or a pregabalin large dosage intake (10)	Common presenting withdrawal features: muscular hyperactivity, hyperthermia, metabolic derangements, rhabdomyolysis, convulsions and delirium; hallucinosis possible (29)	> 100 mg (29)
Antidepressants	Bupropion: amphetamine-like 'high' at mega dosages; acute typical symptoms include: tachycardia, seizures, agitation/irritability, hallucinations/delusions, and tremor (40) Venlafaxine: may mimic MDMA/ecstasy effects; stimulant properties have been described as well (40)	Bupropion: elicits cocaine-like cues; when discontinued, cravings, anxiety, and depression may be observed (40) Venlafaxine: withdrawal symptoms may include: nausea, depression, suicidal thoughts, disorientation, stomach cramps, panic attacks, sexual dysfunction, headaches and occasional psychotic symptoms. (40)	Bupropion: up to 4050 mg/day; oral, nasal/insufflation, and intravenous use (40) Venlafaxine: 2,100-4,050 mg for the purpose of achieving either a dissociative mindset or an 'amphetamine-like' high (38)
Ketamine and related drugs	Sought-after psychoactive effects: dissociative state of mind; perceptual distortions; out-of-the-body (OBE) and near-death (NDE) experiences (46)	Withdrawal symptoms may include: cravings; moderate-to-severe depression and anxiety symptoms (46)	Recreational use: '…Start with 40mg-50mg….100mg is good for dissociative experience, where 200mg-250mg is a really high dose that can send you into an K-Hole…' (44)
Antipsychotics	Quetiapine: anecdotally considered to 'come off the psychedelic trip', and for the desire of 'feeling mellow' (47) Olanzapine: anecdotally reported as the 'ideal trip terminator/modulator' after a psychedelic drug binge. For those on methadone maintenance, olanzapine being used to 'get stoned' (49)	Quetiapine withdrawal syndrome: anxiety; agitation; possibility of movement disorders and supersensitivity psychosis (1)	Quetiapine dosages in excess of 800-1000mg; intake modalities: oral. nasal insufflation of crushed tablets, intravenous (51) Olanzapine: up to 50-100 mg (49)
Gabapentinoids	Euphoric and dissociative effects; pregabalin perceived as an 'ideal psychotropic drug' to achieve specific mindsets, including relaxation and disinhibition (55)	Withdrawal features: anxiety, insomnia, panic; suicidal ideation; chest pain, muscle weakness; possible dyspnoea, palpitations, and dizziness (55)	Pregabalin: 1,500-12,000 mg Gabapentin: 1000–4800 mg (29; 55)
Loperamide	Loperamide ingestion has been associated with euphoria ('lope dope'; 'poors' methadone'), central nervous system depression and even death, due to cardiac dysrhythmias (60)	Opiate/opioid including loperamide withdrawal features: muscle aches; restlessness; anxiety; lacrimation; runny nose; excessive sweating; insomnia; yawning; diarrhoea; abdominal cramps; goose bumps on the skin; nausea and vomiting; dilated pupils; tachycardia and hypertension (59)	Loperamide: doses of 50–1,200 mg. To increase its low bioavailability levels, normally at <2%, 'lope' being associated with: quetiapine, oxycodone;

			SSRIs; grapefruit juice; and tonic water (60)

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