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Review Article

Managing young people with Type 1 diabetes in a 'rave' new world: metabolic complications of substance abuse in Type 1 diabetes

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Abstract

The taxing transition from adolescence towards adulthood intensifies the impact of a chronic illness such as Type 1 diabetes. It is not uncommon for young people with Type 1 diabetes to use recreational drugs for emotional relief to escape the day-to-day burden of chronic disease. Despite increasing use, especially in the setting of 'rave' parties, there is professional lack of understanding of the impact of recreational drug use on glycaemia and metabolic complications. The current review describes the prevalence of substance abuse in Type 1 diabetes and the acute impact of designer drugs on its management. We propose a practical approach to improve care of young people with Type 1 diabetes using designer drugs.

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Keywords Type 1 Diabetes, substance abuse, ketoacidosis, ketamine, cocaine

Abbreviations AKG, acidosis–ketosis gap; DKA, diabetic ketoacidosis; MDMA, methylenedioxymethamphetamine; NDMA, *N*-methyl-D-aspartate

Introduction

Designer drugs have gained increasing popularity amongst young people, especially during 'rave' parties [1]. Despite scattered case reports, little is known about how designer drugs affect young people with Type 1 diabetes. The current review describes the prevalence of designer drug use in Type 1 diabetes, their acute impact on management and a practical approach to improve care in such people.

Prevalence of substance abuse in Type 1 diabetes

Only four studies report the prevalence of substance abuse in young people with Type 1 diabetes. Most used structured questionnaires, with response rates of 54–99% [2–5]. The reported lifetime prevalence of drug use in Type 1 diabetes in these studies was 5–25% in adolescents aged 12–20 years [2–4] and 29% in young adults aged 16–30 years [5]. Cannabis and stimulants were the most popular drugs used. Table 1 summarizes the frequency of drug use from these studies.

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While subjects from some studies were recruited from specialized diabetes clinics [3,5], which may bias frequency of drug use, they highlight a significant problem of substance abuse in some young people with Type 1 diabetes. In addition, underestimation in clinical studies investigating drug-taking prevalence is very likely, perhaps for fear of retribution. Spontaneous confession to drug taking is seldom volunteered, partly because of inadequate routine questioning in acute illness. More than 50% of young adults (mean age 21 years; range 17–24) with diabetes who presented with diabetic ketoacidosis (DKA) to a tertiary referral hospital in a 10-month period admitted to using cannabis (80%), ecstasy (60%), ketamine (60%), benzodiazepines (30%) and heroin (30%); 70% were poly-drug users. However, a drug history was only volunteered in 20% initially and became apparent only with more persistent questioning [6].

Metabolic complications in diabetes

Designer drugs have varied central effects, ranging from hallucinations and psychedelic effects to depression, dissociation and near-death experience. Their effects on glycaemia and metabolic complications in young people with

Table 1 Prevalence of substance abuse in young people with Type 1 diabetes

Authors	Subjects (age, years)	Prevalence (%)	Cannabis (%)	Cocaine (%)	Amphetamine (%)	Ecstasy (%)	LSD (%)	Solvents (%)	Poly-drug users (%)
Glasgow *et al.* [2]	101 (12–20)	25	13	1	6	NR	NR	5	NR
Gold & Gladstein [3]	79 (11–25)	9	10	5	NR	NR	NR	9	NR
Martinez-Aguayo *et al.* [4]	193 (13–20)	10	9.6	2.7	2.7	1.1	NR	NR	NR
Ng *et al.* [5]	85 (16–30)	29	28	12	8	5	2	2	15

LSD, lysergic acid diethylamide; NR, not reported.
Percentage in each drug category represents prevalence of reported use in all questionnaires, except results for Martinez-Aguayo *et al.* [4] which presented lifetime prevalence.

Type 1 diabetes are only described in the literature in case reports or retrospective series. Table 2 summarizes the pharmacology, properties and major effects of popular designer drugs on Type 1 diabetes. Each drug is discussed briefly below.

Methylenedioxymethamphetamine (MDMA)

MDMA, commonly known as ecstasy, is the most popular amphetamine analogue. Ecstasy modulates central serotonergic activity by reducing serotonin synthesis and reuptake and increasing serotonin release. It also affects dopamine and noradrenaline actions [7,8]. The net effect is initial euphoria, but depressive symptoms can occur with large doses, as a result of depletion of neuronal serotonin store (Table 2).

In Type 1 diabetes, ecstasy can precipitate both hyponatraemia and ketoacidosis [1,9]. Hyponatraemia is a well-recognized complication of ecstasy intoxication, attributed to a combination of the syndrome of inappropriate antidiuretic hormone (SIADH) [10–13], polydypsia [14] and proximal renal tubulopathy [15]. Clinical presentation ranges from mild reversible cases to seizures and death [10–12,16].

Ketamine

Ketamine is an arylhexylamine analogue, which acts as an *N*-methyl-D-aspartate (NDMA) receptor antagonist, closely related to phencyclidine (PCP). It reduces excitatory neurotransmission by blocking calcium channels at NDMA receptors [8]. The effects of ketamine are dose-dependent, ranging from a state of relaxation, dissociation and depersonalization known as 'K-land' to a sensation of near-death experience called 'K-hole' [17]. Severe intoxication is characterized by a state similar to malignant hyperthermia, with hypertension, hyperthermia, tachycardia and seizures and an increased mortality [18,19].

Ketamine can precipitate DKA in Type 1 diabetes [1,20]. The metabolic acidosis is severe and disproportionate to the degree of ketosis [20] and, in some cases, associated with rhabdomyolysis. Metabolic acidosis without DKA has also been reported with ketamine use [21].

Opioid analogues

While most clinicians are familiar with opioids such as heroin, new synthetic analogues of fentanyl and meperidine are used increasingly for their heroin-like effects. Such derivatives are much more potent than heroin and fatal cases are reported from misuse and ignorance of its high potency [22].

There is a paucity of literature on the impact of heroin on Type 1 diabetes. We previously reported an unusual presentation of hyperglycaemic hyperosmolar state (plasma glucose 108 mmol/l) in the absence of acidosis following heroin overdose [16]. Lethal levels of methadone have also been reported in a patient who died of DKA [23].

Cocaine

Cocaine is a potent stimulant and an indirect sympathomimetic agent, which exerts its effects on the cardiovascular system through α- and β-receptor agonism. Its euphoric effects relate to serotonin, dopamine and noradrenaline reuptake inhibition [24]. Hyperglycaemic hyperosmolar state is a known complication of cocaine use [25–27]. A recent retrospective analysis demonstrated cocaine abuse to be the strongest independent risk factor of recurrent presentation of DKA [27].

Cannabis

Cannabis is the most commonly used recreational drug in young people with Type 1 diabetes (Table 1). There has been extensive research in recent years into the role of cannabinoids in health and disease [28]. Although the impact of acute administration of cannabis, as smoked marijuana, on glucose metabolism is minimal [29], impaired judgment following acute use may cause insulin non-compliance. As cannabis can stimulate appetite ('munchies'), it may lead to hyperglycaemia, especially in

Table 2 Summary of pharmacology and effects of designer drugs on metabolic aspects of Type 1 diabetes

Drug	Street names	Form	Pharmacology	Clinical effects	Complications
MDMA	Ecstasy, E, love's speed, essence, X-TC, Adam, clarity, Stacy	Capsule, tablet > powder (snorted/smoked)	↑ serotonin activity	Euphoria, derealization, depersonalization, anxiety, ataxia, polydipsia	DKA, hyponatraemia, SIADH, seizure, death
Ketamine	'K', Vitamin K, 'Special K', cat valium	Powder (snorted/smoked), liquid (injected), tablet	NDMA receptor antagonist	Euphoria, relaxation, depersonalization, hypertension, hyperthermia	DKA, metabolic acidosis, seizure, death
Opioid analogue	Mexican brown, Persian white, China white	Injected, snorted, smoked	Opioid agonists	Euphoria, central and respiratory depression	Hyperglycaemia, DKA, death
Cocaine	—	Smoked, snorted > ingested	Indirect sympathomimetic agent	Euphoria, relaxation	Hyperglycaemia, DKA

DKA, diabetic ketoacidosis; MDMA, methylenedioxymethamphetamine; NDMA, *N*-methyl-*D*-aspartate; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

the setting of rave parties when glucose-laden drinks are consumed without appropriate insulin adjustment.

Others

The effects of newer designer drugs such as methcathinone analogues, methaqualone analogues and herbal designer drugs such as diphenhydramine containing compounds ('green hornet') are unknown.

Mechanisms of drug effects

Hyperglycaemia, ketosis and acidosis in different combinations and severity are the main toxic effects of designer substance abuse in people with Type 1 diabetes. However, many published reports are descriptive and retrospective. Designer drugs are synthesized illegally in clandestine laboratories, with variation in contents and contaminants. Understandably, there have been no well-controlled studies investigating the mechanisms of toxicity in Type 1 diabetes. We postulate several mechanisms for toxicity, based on the known pharmacology of these drugs and our experience (Fig. 1).

Catecholamine toxicity

Most of the drugs associated with substance abuse are stimulants and are associated with sympathetic overactivity, manifesting predominantly as hypertension and tachycardia [7,30]. Methamphetamine is the most studied in this category, with its cardiovascular toxicity attributed to elevated catecholamine levels in human studies [31,32] and animal models [33,34]. Direct methamphetamine cardiotoxicity, independent of catecholamines, has also been reported [35]. Elevated catecholamines can result in hyperglycaemia, by inhibiting insulin secretion [36],

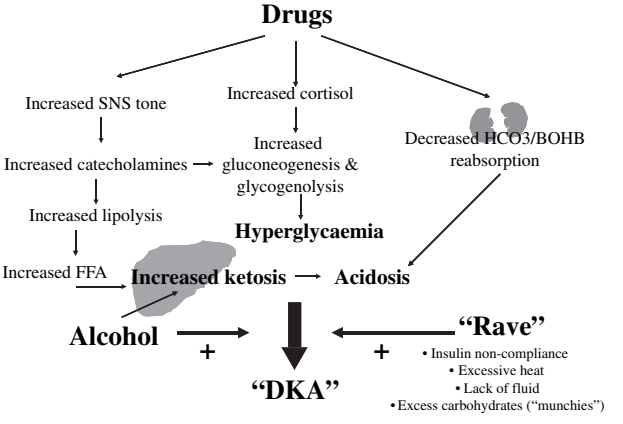

FIGURE 1 Schematic diagram of possible mechanisms of designer drug-related toxicity in people with Type 1 diabetes. DKA, diabetic ketoacidosis; FFA, free fatty acid; HCO3/BOHB, bicarbonate/beta-hydroxybutyrate; SNS, sympathetic nervous system.

increasing hyperglucagon secretion [37] and enhancing gluconeogenesis [38] and glycogenolysis [39,40].

Animal studies have demonstrated hyperglycaemia following ketamine [41,42] and heroin [43] administration. Plasma glucose concentrations were higher in heroin users following oral glucose challenge and were accompanied by significant hypoinsulinaemia [44]. A recent study also demonstrated hypoinsulinaemia in non-diabetic subjects following cocaine administration [45].

Enhanced lipolysis

Young people with Type 1 diabetes have significant risk of ketosis when using stimulants. Ketoacids are produced during hypoinsulinaemia in the liver when levels of anti-insulin hormones, such as cortisol, catecholamine and glucagon, are elevated. Serum cortisol, for example, is elevated acutely in MDMA users [46,47]. In addition, activation of the sympathetic nervous system by drugs of abuse can stimulate β_2-adrenoceptor mediated lipolysis, with increased availability of fatty acids determining the extent of ketoacid production [48,49]. During a 'rave', under the influence of mood-enhancing drugs, young people may dance for long periods without food; fasting further increases the risk of ketosis.

Altered renal 3-hydroxybutyrate and bicarbonate handling

The combined effects of drugs on the enhancement of hyperglycaemia and ketosis provide the dangerous milieu for the development of DKA. However, while DKA is a common complication of substance abuse in Type 1 diabetes, not all hyperglycaemia leads to DKA [16] and not all metabolic acidosis is as a result of DKA [6,20]. The reason for lack of acidosis in severe hyperglycaemia in Type 1 diabetes in some cases with substance abuse is not known [16].

Ketamine causes severe metabolic acidosis with relatively mild ketosis [20], which is characterized by an elevated acidosis–ketosis gap (AKG) [6]. Metabolic acidosis disproportionate to the degree of ketosis may be explained by altered renal handling of ketone bodies and bicarbonate [6]. Substances such as L-lactate and salicylic acid can impair renal β-hydroxybutryate reabsorption [50]. As drug users have significantly lower serum bicarbonate and β-hydroxybutryate concentrations, one may speculate that drug-induced renal bicarbonate and β-hydroxybutyrate wasting causes significant acidosis and relatively low plasma β-hydroxybutyrate levels. This is congruent with the findings of lower Δ anion gap/Δ bicarbonate in drug users [6]. It is important to exclude glue-sniffing by measuring serum hupuric acid or tulene levels and co-existent renal tubular acidosis, as these conditions may present with a similar biochemical picture [51,52].

Contamination of cannabis by other substances, such as lead, is another possible contributor to metabolic acidosis. Acute lead toxicity was reported recently as a result of adulterated marijuana [53]. Chronic lead poisoning can cause lead nephropathy associated with hyporeninaemic hypoaldosteronism and metabolic acidosis [54,55].

In a 'rave' new world

The risk of hyperglycaemia, ketosis and acidosis in Type 1 diabetes is magnified in the setting of a 'rave', which is an all-night dance party where 'mood-enhancers' are freely used, including the popular designer drugs discussed previously [56]. People with Type 1 diabetes are particularly vulnerable to the metabolic and toxic drug effects at such parties. Insulin non-compliance is common; coupled with the consumption of glucose-laden drinks and toxic effects of stimulants on hyperglycaemia and ketosis, the risk of DKA is increased. Although alcohol is commonly banned in a 'rave', concurrent alcohol consumption further increases the risk of ketosis [57].

Management

Longitudinal cohort studies demonstrated a poor prognosis in young diabetic patients transiting into adulthood, with the poorest glycaemic control observed in the 16- to 18-year age group [58,59]. Mortality from acute events such as DKA was not associated with classic complications such as nephropathy, neuropathy, hypertension and retinopathy in young adults with Type 1 diabetes. However, a past history of drug abuse was associated with death from acute diabetes-related events, with an odds ratio of 5.7 [60]. Management of substance abuse in young people with Type 1 diabetes should be based on an open, non-judgemental approach. History taking should routinely include questions on substance abuse, as non-reporting and under-reporting are common [5,6].

Prompt commencement of insulin-infusion protocols can resolve hyperglycaemia and ketosis, but metabolic acidosis should be carefully examined to exclude drug-related non-ketotic causes. While other causes of acidosis such as lactate and renal failure are now detected with biochemical markers, designer drug toxicity is easily missed if clinicians do not have a high index of suspicion. The biochemical picture of drug toxicity with hyponatraemia, hyperglycaemia, ketosis, metabolic acidosis and renal impairment are often indistinguishable from an uncomplicated presentation of DKA. Atypical features, such as evidence of sympathetic overactivity (which may be masked by concurrent benzodiazapine use), potassium and/or phosphate wasting and elevation of creatine kinase, should raise the suspicion of drug use.

As history taking can be unreliable in patients with an altered conscious state or in victims of drink spiking, urinary drug screen should be performed if there is any clinical suspicion. As results of drug screens can be delayed, we have

advocated calculation of the AKG (arterial pH–plasma β-hydroxybutryrate) to help identify drug use as a contributor to DKA. An AKG of > 3 was found in 80% of drug users, compared with only 33% of non-drug users [6].

Parties are an important part of young people's social lives. Management should therefore focus on harm minimization, rather than advocating abstinence. Alternative insulin regimens for young people over social weekends accommodating dietary modifications seem appropriate. Action plans based on capillary glucose and ketone bodies recorded during the night can be life saving.

Conclusion

This review cannot provide recommendations for all people with Type 1 diabetes, as each situation is unique and all interactions of designer drugs cannot be generalized. However, we advocate increased awareness of the impact of drug use on Type 1 diabetes, as consequences may be fatal. Although non-compliance and infection are classic DKA precipitants, substance abuse should be considered even without suggestive history, particularly with atypical biochemical features. The provision of better health care to young patients with Type 1 diabetes relies on acceptance that poly-drug use occurs and it is time for the clinician to be educated in the management of this under-appreciated health issue.

Competing interests

Nothing to declare.

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