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Acute psychotropic, autonomic, and endocrine effects of 5,6-methylenedioxy-2-aminoindane (MDAI) compared with 3,4-methylenedioxymethamphetamine (MDMA) in human volunteers: A self-administration study

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Abstract

The acute psychoactive, autonomic, and endocrine effects of the new psychoactive substance (NPS) 5,6-methylenedioxy-2-aminoindane (MDAI; 3.0 mg/kg, range 180–228 mg) were investigated in six healthy volunteers (four males, two females) in a non-blinded fashion without placebo. Subjective, cardiovascular, and endocrine responses were compared with two different doses of 3,4-methylenedioxymethamphetamine (MDMA) (75 mg and 125 mg) described in previously published placebo-controlled studies, which used identical outcome measures including Visual Analogue Scales (VAS), the Adjective Mood Rating Scale (AMRS), and the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale. MDAI was well tolerated and produced subjective effects comparable with those of 125 mg MDMA. MDAI increased blood pressure similar to 125 mg MDMA but did not increase heart rate or body temperature. MDAI increased cortisol and prolactin levels and could be detected in serum about 20 min post ingestion and remained detectable at least for 4 days. In urine, MDAI was detectable over a period of at least 6 days. Further clinical investigations are warranted to assess whether MDAI could serve as drug with medicinal properties.

KEYWORDS

clinical, entactogens, new psychoactive substances, pharmacokinetics, psychometric

Verena Angerer and Yasmin Schmid have contributed equally to this manuscript.

1 | INTRODUCTION

The emergence of new psychoactive substances (NPS) has attracted the attention of policy makers, regulatory institutions, healthcare providers, and researchers across the globe. A highly dynamic and typically poorly regulated market has evolved around the manufacturing and supply of psychoactive compounds. One of the many striking facets can be seen in the chemical and pharmacological diversity associated with NPS, which essentially reflects the intersections found between controlled substances, medicines (including failed or unexplored drug development endeavors), dietary supplements and "designer drugs".[1–4] One stimulus for entrepreneurs and manufacturers to develop ideas for marketing has always included the systematic search of existing patent and academic research literature and to stretch the imagination beyond non-clinical research data.

One substance that appeared on the NPS market around 2010[5–8] was 6,7-dihydro-2*H*,5*H*-indeno[5,6-*d*][1,3]dioxol-6-amine (5,6-methylenedioxy-2-aminoindane, MDAI) (Figure 1), which originated from research into the pharmacological properties of substances related to 3,4-methylenedioxymethamphetamine (MDMA) and monoamine signaling.[9,10] Following its appearance around 2010, it soon also became available for purchase from Internet retailers that resulted in detections in products obtained online, though it appeared that its availability on the market was limited.[11–18] MDAI has occasionally been detected in biological samples obtained from treatment clinics, intoxications, and death cases although other substances have also been detected in some of these.[19–23] In other cases, unambiguous confirmations involving toxicological analysis were not reported.[24,25]

One potential reason for its original appearance on the market might have been based on the assumption that MDAI would show MDMA-like effects in humans when attempting to interpret non-clinical research data. MDAI was developed and explored in the early 1990s by the Nichols group.[26–31] One important element of this work arose from the investigation of mechanisms associated with monoamine signaling and serotonin depletion observed with MDMA and early findings indicated that MDAI showed reduced neurotoxicity when compared with MDMA.[26,29,31] Other aminoindane derivatives have also been explored since then,[9,10] but MDAI was one of the analogs that began to diffuse into the NPS market comparatively early though it appeared to have a short-lived lifespan compared with many other substances.

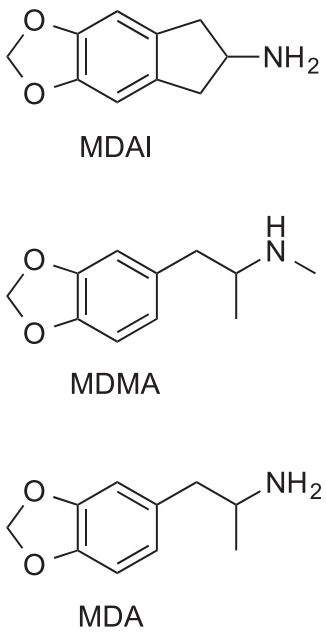


FIGURE 1 5,6-Methylenedioxy-2-aminoindane (MDAI), 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA).

The information available on MDAI (essentially a cyclized analog of 3,4-methylenedioxyamphetamine [MDA]) suggests that it shares key pharmacological similarities with MDMA. For example, in vivo studies involving drug discrimination revealed that MDAI substituted for the discriminative stimulus properties of MDMA and 1-(2*H*-1,3-benzodioxol-5-yl)-*N*-methylbutan-2-amine ([+]-MBDB) but not (*S*)-amphetamine or lysergic acid diethylamide (LSD).[26,27,30,32,33] MDAI was also reported to fully substitute for 2,5-dimethoxy-4-methylamphetamine (DOM) and cocaine though drug-appropriate responding in methamphetamine-trained rats was only 73%.[33] Similar to MDMA,[34] in vitro studies have shown that MDAI acts at serotonin (SERT), dopamine (DAT), and norepinephrine transporters (NET).[28,35–38]

Some anecdotal reports on the subjective effects of MDAI exist on various Internet forums,[10,20] but physiological and psychometric data obtained from human volunteers are not available. Though the practice of self-administration is less frequently encountered in scientific studies nowadays, it is also clear that critical information can be obtained from such exploratory studies.[39] In order to address the question whether MDAI does indeed show MDMA-like properties in humans, a non-blinded non-placebo study was designed to assess acute pharmacodynamic and preliminary pharmacokinetic outcome measures following a single oral administration of 3.0 mg/kg MDAI to six healthy volunteers. In comparison with MDMA, the evaluations included the assessment of physiological and endocrine measures, the analysis of urine and serum samples by liquid chromatography tandem mass spectrometry and application of psychometric instruments such as the Visual Analogue Scales (VAS), the Adjective Mood Rating Scale (AMRS), and the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale.

2 | EXPERIMENTAL

2.1 | Chemicals and reagents

Methanol, dichloromethane, ammonia, and 2-propanol were of gradient grade and were obtained from J.T. Baker (Deventer, Netherlands) and Carl Roth (Karlsruhe, Germany). Ammonium formate was supplied by Sigma-Aldrich (Steinheim, Germany) acetonitrile and formic acid by Carl Roth (Karlsruhe, Germany). Deionized water was prepared using a cartridge deionizer from Memtech (Moorenweis, Germany). Deuterated MDMA (MDMA-D_5) was purchased from LGC Standards (Wesel, Germany). MDAI HCl was bought as a "research chemical" over the Internet. The identity and purity (approx. 98%) was verified using ^{1}H

and ^{13}C nuclear magnetic resonance spectroscopy (NMR), gas chromatography electron ionization mass spectrometry (GC-EI-MS), and liquid chromatography tandem mass spectrometry (LC-ESI-MS/MS). The solid phase extraction cartridges Chromabond® Drug were obtained from Macherey Nagel (Düren, Germany).

2.2 | Sample preparation

After adding 10 µl internal standard (MDMA-D_5, 1 µg/ml) and 2 ml of phosphate buffer (pH 6) to 1 ml of urine or serum, the samples were extracted using a Chromabond® Drug solid phase extraction cartridge. The cartridges were conditioned with 2 ml methanol and 2 ml phosphate buffer (pH 6) before the supernatant of the samples was subjected to gentle evaporation. The samples were washed using 2 ml deionized water, 1 ml acetic acid (0.1 M), and 2 ml methanol and dried under vacuum for 10 min. The analytes were then eluted with 1.5 ml of dichloromethane/2-propanol/ammonia (40/10/1, *v/v/v*). The eluate was evaporated under a stream of nitrogen at 40°C followed by addition of 100 µl 2-propanol/hydrochloric acid (3/1, *v/v*) just before the solution was completely evaporated. The mixture was then evaporated to dryness. The residue was reconstituted with 100 µl mobile phase A/B (99/1, v/v). Solvent A was water with 0.1% formic acid and 10 mM ammonium formate. Solvent B was methanol containing 0.1% formic acid.

2.3 | Instrumentation and method of analysis

The samples were analyzed using liquid chromatography coupled to a QTrap 4000® tandem mass spectrometer (Sciex, Darmstadt, Germany). Separation was achieved using a Synergi Polar-RP column (100 mm × 2 mm, 2.5 µm) with an equivalent guard column (4 mm × 2 mm; Phenomenex, Aschaffenburg, Germany). Column oven temperature was set at 40°C, gradient elution was performed using the following gradient: 0–5 min: 1% B–7.5% B; 5–12.5 min: 7.5% B–50% B; 12.5–14.5 min: 50% B–90% B; 14.5–16.5 min: 90% B; 16.5–17 min 90% B–1% B; 17–25 min: 1% B. The flow rate was 0.4 ml/min and 2-propanol was added post-column with a flow of 0.1 ml/min.

2.4 | Administration of 5,6-methylenedioxy-2-aminoindane (MDAI) to healthy volunteers

The effects of MDAI HCl (3.0 mg/kg) were assessed in a non-blinded, non-placebo controlled study in six healthy subjects (two females, four males; mean ± SD age of 33.0 ± 5.6 years). The data were directly compared with the data of previously published studies on the effects of MDMA, which were assessed in double-blind, placebo-controlled cross-over studies using either a dose of 125 mg of racemic MDMA HCl (corresponding to a mean ± SD dose of 1.9 ± 0.2 mg/kg) and placebo in 16 subjects (eight women, mean ± SD age of 24.8 ± 2.6 years[40]) or 75 mg of MDMA (corresponding to a mean ± SD dose of 1.1 ± 0.13 mg/kg) and placebo in 30 subjects (15 women, mean ±SD age of 24 ± 4.2 years[41]). The MDMA studies were conducted in accordance with the Declaration of Helsinki and International Conference of Harmonization Guidelines in Good Clinical Practice (GCP) and were approved by the local Ethics Committee. The MDMA studies were registered at ClinicalTrials.gov (NCT01465685 and NCT01616407). Subjects provided written informed consent before participating in these studies and were paid for their participation. Identical outcome measures including autonomic and subjective drug effects allowed for a comparison of MDAI with different doses of MDMA. All six participants of the MDAI study are coauthors of this publication and had no history of drug dependence. Four out of six had used cannabis at some time in their lives, and two had sporadic previous experience with other illicit drugs several years ago ("ecstasy", cocaine, and hallucinogens). In Germany, approval by an Ethics Committee is not required for scientific self-experiments.

MDAI was administered orally as a single dose of 3.0 mg/kg body weight, corresponding to a mean ± SD dose of 212.5 ± 20.0 mg (range 180–228 mg). Urine samples were collected over a period of 11 days; each urine of the day of the experiment and of the following day and afterwards every morning urine over a period of 9 days. Moreover, 12 blood samples were collected during the day of the experiment, and seven blood samples were collected on the following 5 days. The design of the MDMA studies has previously been published in detail.[40,41] Briefly, MDMA (75 mg or 125 mg) or placebo were administered at 9 am to healthy mostly MDMA-naïve subjects and subjective, autonomic, and endocrine effects were repeatedly measured.[40,41] Histories of use of drugs of abuse were as follows: in the MDMA studies, 40 subjects had used cannabis at some time in their lives, and 18 subjects had minimal previous experience with other illicit drugs (2–4 times) including "ecstasy" (n = 14), stimulants (n = 9), hallucinogens (n = 5), and nitrous oxide (n = 3).

2.5 | Pharmacodynamic outcome measures

2.5.1 | Psychometric scales

Subjective measures included VAS,[42] the AMRS,[43] and the 5D-ASC scale.[44] VAS were presented as 100 mm horizontal lines marked with "not at all" on the left and "extremely" on the right. The VAS for "open", "trust", and "closeness" were bidirectional (±50 mm). The 5D-ASC dimension "Oceanic Boundlessness" (OB, 27 items) measures derealization and depersonalization phenomena associated with positive emotional states ranging from heightened mood to euphoric exaltation. The corresponding lower order scales were "experience of unity", "spiritual experience", "blissful state", "insightfulness", and "disembodiment". The dimension "Anxious Ego Dissolution" (AED, 21 items), gauged ego-disintegration and loss of self-control phenomena associated with anxiety. The corresponding lower order scales were "impaired control of cognition" and "anxiety". The dimension "Visionary Restructuralization" (VR, 18 items) consisted of the lower

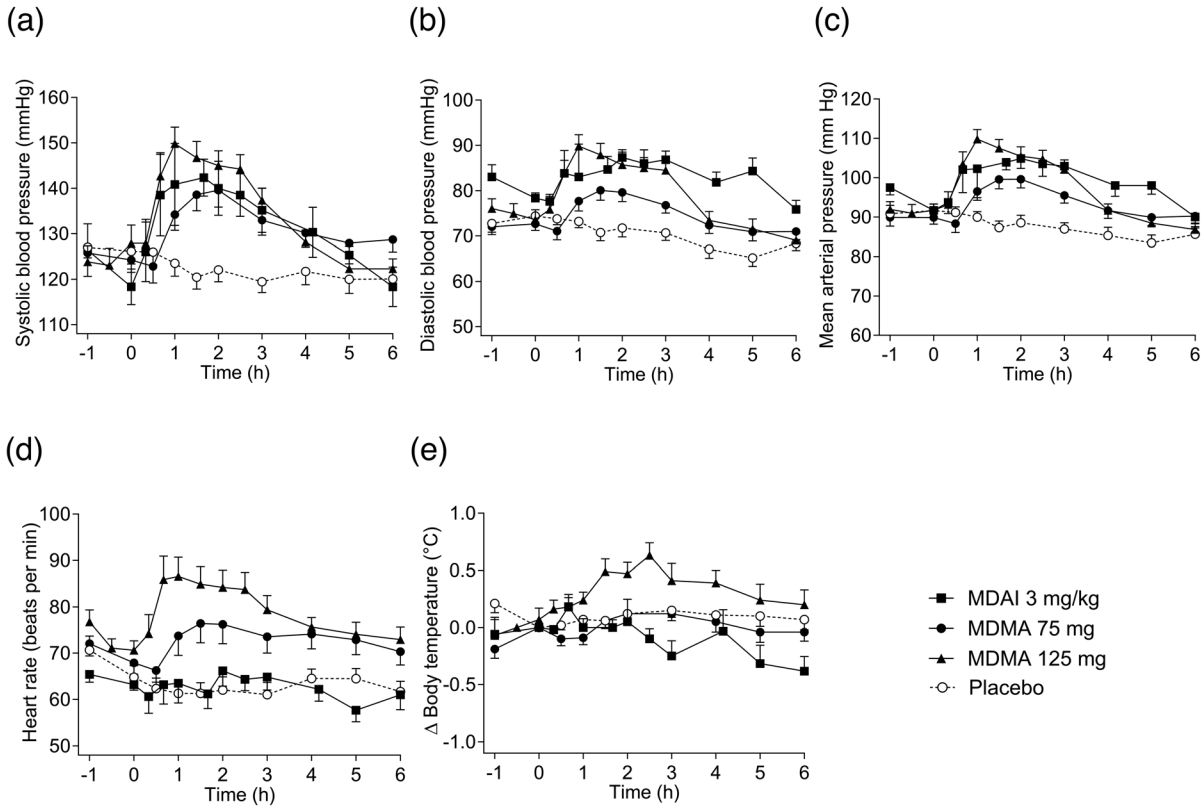


FIGURE 2 Vital signs over time. MDAI, MDMA 125 mg, and MDMA 75 mg were administered at t = 0 h. Overall, a similar time course of changes of vital signs after administration of MDAI and MDMA at different doses can be seen. MDAI increased mean arterial blood pressure (c) similar to the 125 mg dose of MDMA but more than the 75 mg dose of MDMA. The MDAI-induced increase in systolic blood pressure (a) was comparable with both doses of MDMA. However, MDAI produced a higher increase in diastolic blood pressure (b) than the 75 mg dose of MDMA. MDAI did not change heart rate (d) or body temperature (e). The data are expressed as the mean ± SEM in six subjects with MDAI 3 mg/kg, 16 subjects with 125 mg of MDMA, and 30 subjects with 75 mg of MDMA.

order scales "complex imagery", "elementary imagery", "audio-visual synesthesia", and "changed meaning of percepts". Two additional dimensions ("auditory alterations" and "vigilance reduction") were not included in the present study. The global ASC score (3D-ASC total score) was constructed by addition of the OB, AED, and VR scores. The 5D-ASC scale was completed 5 h after MDAI intake. Similarly, ratings on the 5D-ASC scale following MDMA and placebo were assessed 5 h after drug administration in the previous investigations.[40,41]

2.5.2 | Physiological measures

Heart rate and systolic (SBP) and diastolic blood pressure (DBP) were measured repeatedly using an automatic blood pressure monitor in the dominant arm with the volunteer sitting without engaging in physical activity. Core (tympanic) temperature was assessed using an ear thermometer. The first measurement was carried out before drug intake. After drug intake the parameters were measured every 20 min until 1 h post ingestion, then every half hour until 3 h post ingestion and then every hour until 6 h post ingestion. The last measurement was performed in the following morning.

2.5.3 | Endocrine measures

The plasma levels of prolactin and cortisol were measured at baseline and 2 h after drug administration using the Elecsys electrochemiluminescence immunoassays (ECLIA) on the cobas e 801 analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

2.6 | Data characterization

Repeated measures were expressed as peak effects (E_{max}) or peak changes from baseline (ΔE_{max}). Detailed values can be found in the Supporting Information, Table S1.

3 | RESULTS AND DISCUSSION

3.1 | Vital signs

The effects of MDAI and MDMA on vital signs are shown in Figure 2. MDAI increased mean arterial blood pressure similar to the 125 mg

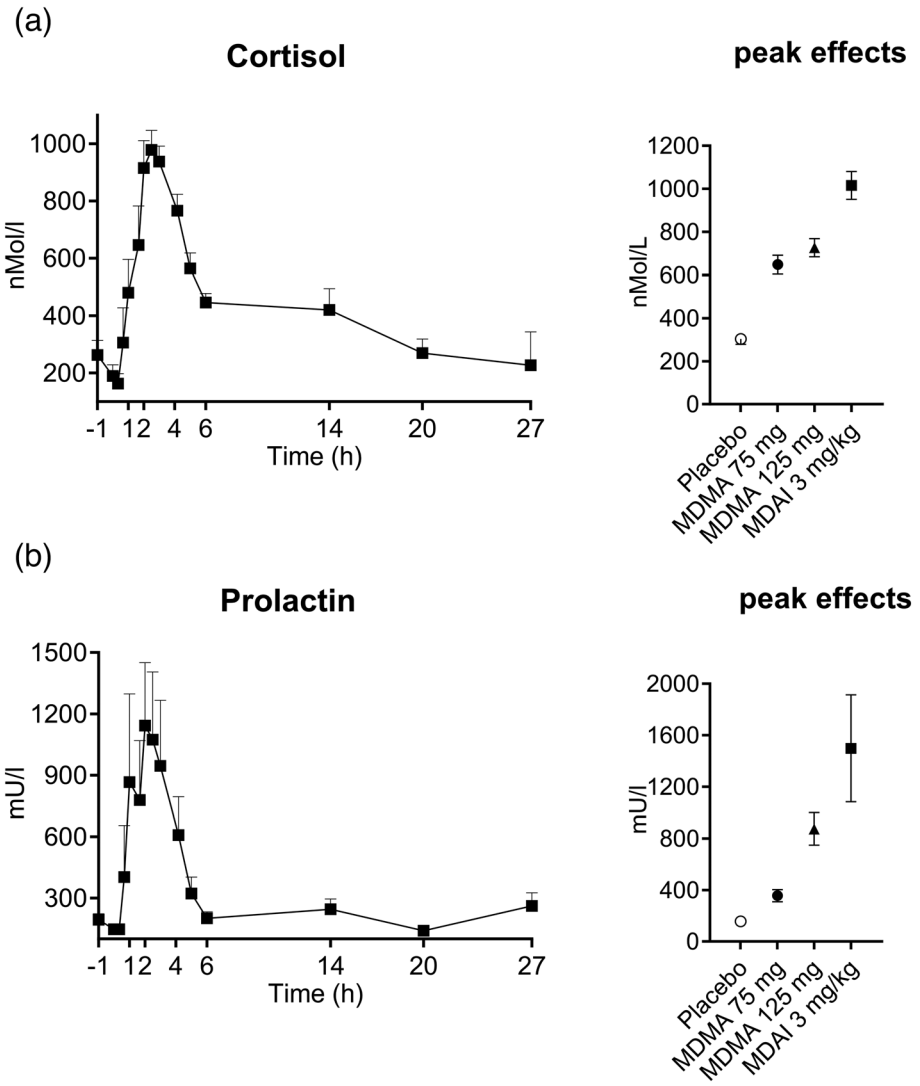


FIGURE 3 MDAI increased plasma cortisol and prolactin. Time courses of plasma concentration of cortisol and prolactin after administration of MDAI at t = 0 h are shown in the left-side panels. Right-side panels show peak plasma levels of cortisol and prolactin after administration of MDAI, MDMA 75 mg, MDMA 125 mg, and placebo. Peak concentration of cortisol (a) and prolactin (b) was higher after MDAI compared with MDMA 75 mg or 125 mg. The values are expressed as the mean ± SEM in six subjects with MDAI 3 mg/kg, 16 subjects with 125 mg of MDMA, and 30 subjects with 75 mg of MDMA.

dose of MDMA but more than the 75 mg dose of MDMA. The MDAI-induced increase in systolic blood pressure was similar to that produced by both doses of MDMA and MDAI produced a greater increase in diastolic blood pressure than the 75 mg dose of MDMA. MDAI did not change heart rate or body temperature although the study lacked a placebo condition to better validate this finding. In controlled clinical settings, increases in tympanic temperature following MDMA administration have been found to be minor ($\Delta T = 0.2–0.8^{\circ}C$) or moderate (>38°C) at higher dosage levels.[45] However, the risk of developing hyperpyrexia at excessive doses and under conditions that affect heat dissipation is likely to be increased. In a recent study, subcutaneous injections of 10 mg/kg and 20 mg/kg MDAI in rats revealed that body temperature and perspiration robustly increased under group-housed conditions but not when animals were housed individually and behavioral observations were consistent with a serotonin behavioral syndrome.[46] The effects on body temperature in rats were more pronounced for MDAI when compared with MDMA. Although the authors concluded that MDAI might pose a higher risk for hyperpyrexia in humans, too, the results obtained in this study did not support this hypothesis under the conditions used.

3.2 | Endocrine effects

MDAI increased plasma levels of both cortisol and prolactin (Figure 3). The C_{max} of cortisol and prolactin was higher after MDAI compared with those levels observed following MDMA 75 mg and MDMA 125 mg. Increases in cortisol and prolactin levels reflected the pharmacological challenge with substances known to induce increased serotonin levels,[47] and it was also observed that the cortisol and prolactin increase was greater than MDMA after MDAI treatment. However, pre-drug hormone levels were lower in the evening when obtained from the MDAI subjects compared with the MDMA study subjects that were evaluated in the morning. In fact, when relative increases in plasma cortisol and prolactin in the MDAI subjects were calculated using values obtained in the morning following the

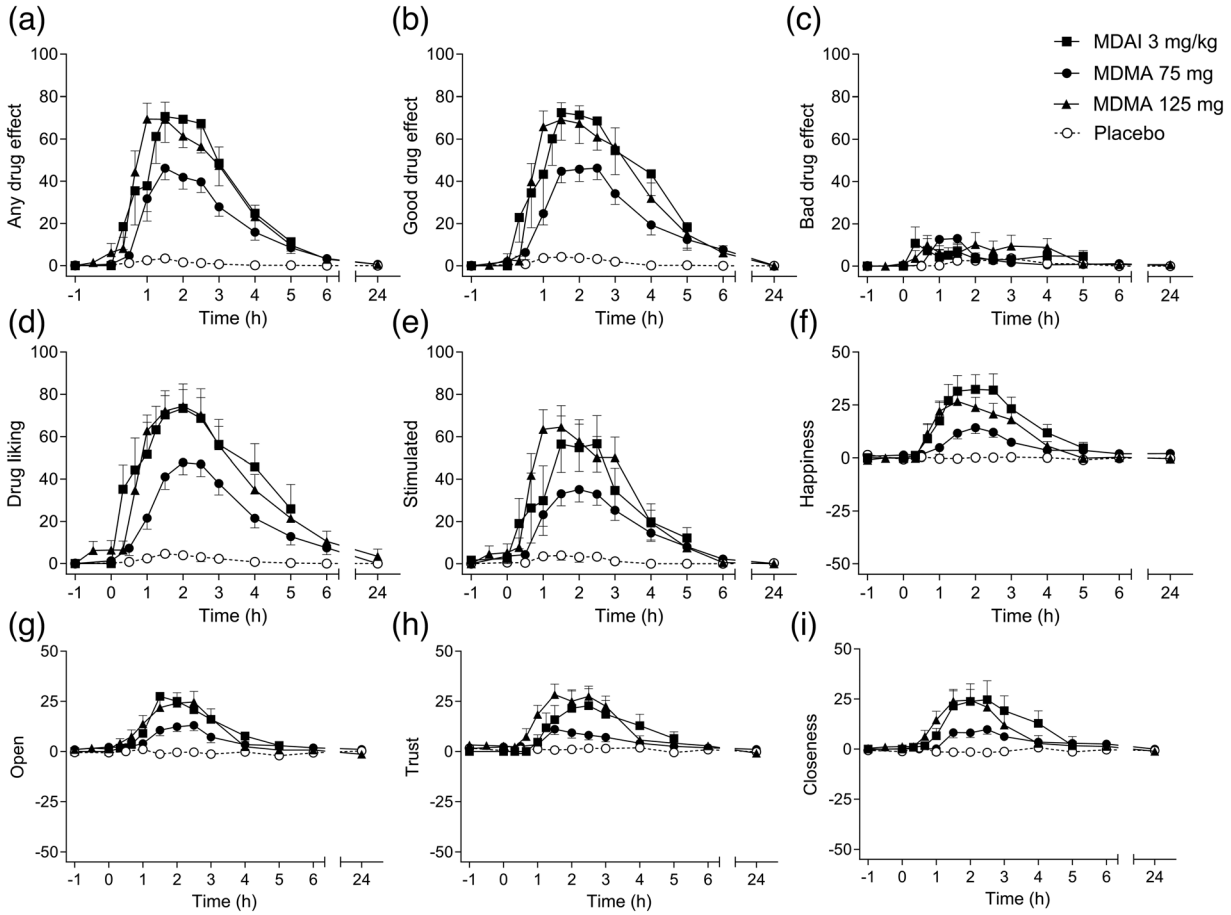


FIGURE 4 MDAI produced similar subjective effects to MDMA. In the VAS, MDAI overall produced identical effects to MDMA 125 mg including strength and time course of the response. MDAI increased ratings of "any drug effect" (a), "good drug effect" (b), "stimulated" (e), "happy" (f), "open" (g), "trust" (h), and "closeness" (i) similar to MDMA 125 mg. Subjective effects of MDAI were greater than those of MDMA 75 mg. The data are expressed as the mean ± SEM in six subjects with MDAI 3 mg/kg, 16 subjects with 125 mg of MDMA, and 30 subjects with 75 mg of MDMA. Drugs were administered at t = 0 h.

experiment in the same subjects, the hormonal changes were similar to those seen with the 125 mg dose of MDMA.

3.3 | MDAI serum and urine concentrations

MDAI could be detected in serum about 20 min post ingestion until about 4–5 days. The maximum serum concentration was measured between 5,000 and 9,000 ng/ml and MDAI could be detected in serum at least for 4 days, and in some subjects, MDAI was detected at concentrations lower than 1 ng/ml (0.18–0.94 ng/ml) after 140 h (5 days) (Supporting Information, Figure S1). In urine, MDAI was detectable over a period of at least 6 days. In some subjects, MDAI could be detected in urine for almost 10 days at concentrations below 1 ng/ml (0.04–0.14 ng/ml). Particularly high amounts of MDAI were detected in the urine sample of one participant (Figure S2), which suggested a genetic variation in the CYP2D6 phenotype (poor CYP2D6 metabolizer)[48] responsible for *O*-demethylation. Whether MDAI displays CYP2D6 autoinhibition similar to MDMA however, remains to be confirmed.[49]

Metabolites of MDAI were not measured because of the long detectability of MDAI in urine (Supporting Information, Figure S2). Recent studies carried out in rats revealed that MDAI reached a maximum median serum concentration of 4.3 mg/l at the 30 min mark following subcutaneous MDAI administration (10 mg/kg) with an estimated elimination half-life of 0.8 h.[46] Following subcutaneous administration of 20 mg/kg in rats, it was also confirmed that the main component identified in urine was unchanged MDAI though other metabolites also were described.[50]

3.4 | Subjective effects

A key feature associated with the psychopharmacological profile of MDMA is the ability to facilitate pro-social effects, heightened states of introspection, and intimacy coupled with reduced fearfulness and increased empathy,[41,47,51–53] which lends itself to its use in therapeutic interventions.[54]

Overall, the subjective effects of MDAI were qualitatively very similar to those of MDMA (Figures 4–6). As determined using VAS, MDAI

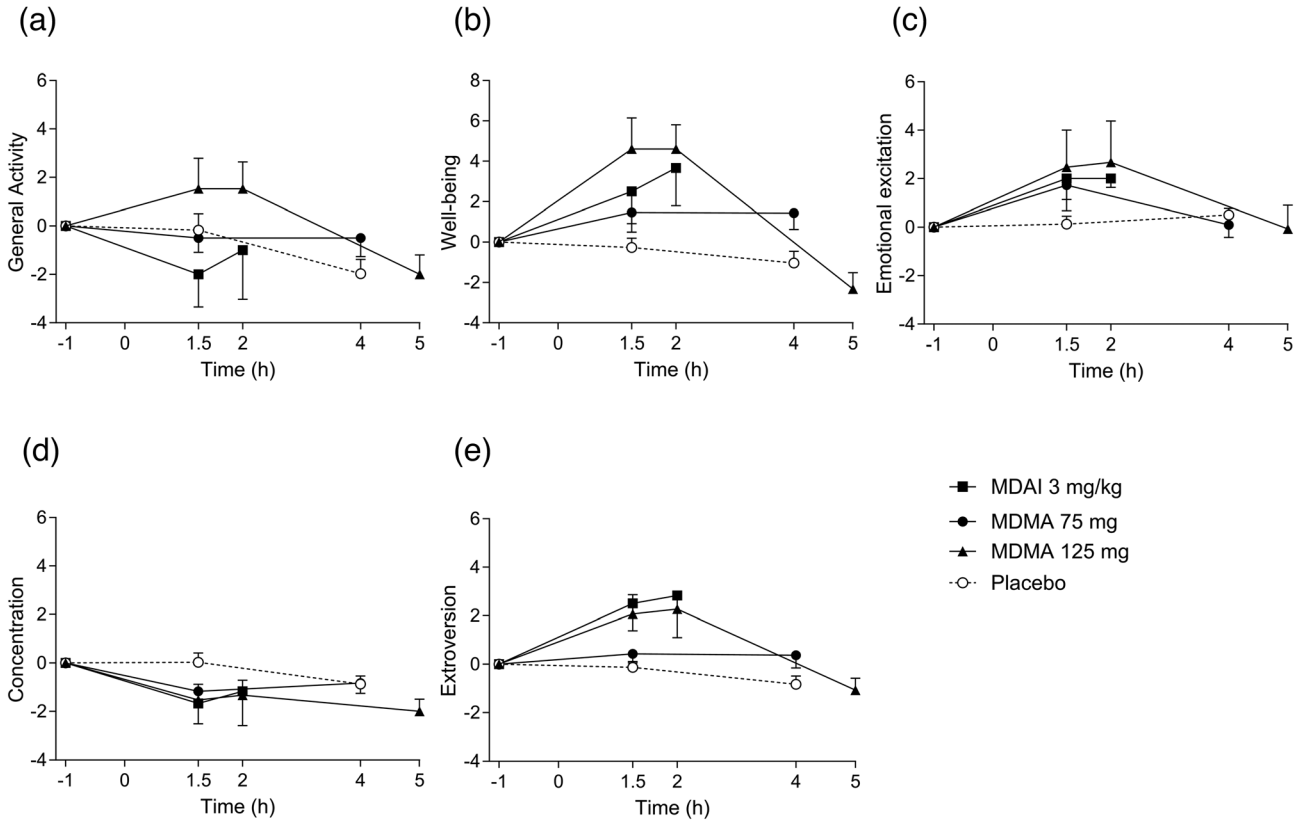
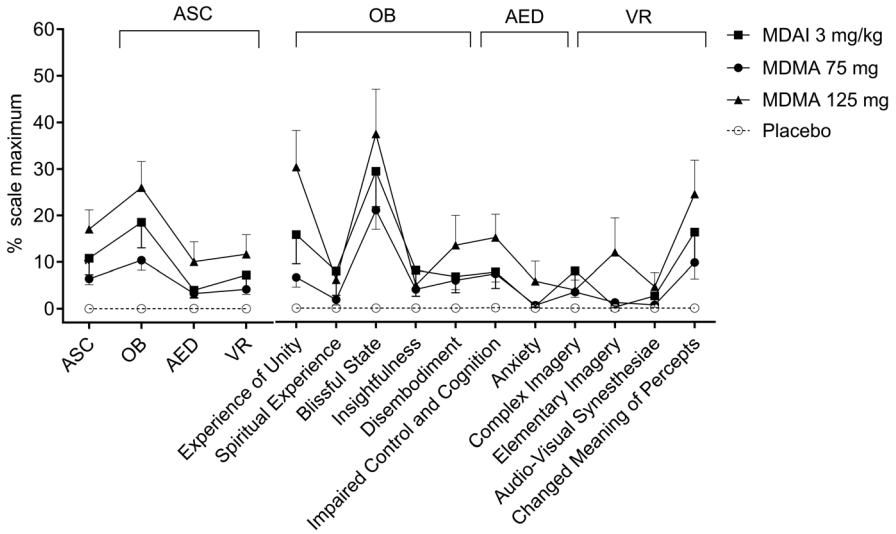


FIGURE 5 MDAI produced similar mood effects to MDMA. In the AMRS, MDAI increased well-being (b), emotional excitation (c), and extroversion (e) but not activity (a) or concentration (d) similar to MDMA. The data are expressed as the mean ± SEM in six subjects with MDAI 3 mg/kg, 16 subjects with 125 mg of MDMA, and 30 subjects with 75 mg of MDMA. Drugs were administered at t = 0 h.

FIGURE 6 MDAI induced an altered state of consciousness similar to MDMA. In the 5D-ASC, MDAI increased the different sub-scores similar to MDMA. MDAI mainly induced a blissful state, experience of unity, and changed meaning of percepts, similar to MDMA. Effects of MDAI were slightly greater compared with MDMA 75 mg and slightly lower compared with MDMA 125 mg. The data are expressed as the mean ± SEM in six subjects with MDAI 3 mg/kg, 16 subjects with 125 mg of MDMA, and 30 subjects with 75 mg MDMA.



produced very similar subjective effects to 125 mg of MDMA, including pleasurable drug effects, drug liking, stimulation, happiness, openness, trust, and closeness (Figure 4). In the AMRS, MDAI increased the sense of well-being, emotional excitation, and extroversion but not general activity and concentration, a profile similar to MDMA (Figure 5). In the 5D-ASC scale, MDAI mostly induced a blissful state, experience of unity, and a changed meaning of percepts, comparable with MDMA (Figure 6). Even though the questionnaires used are able to differentiate between different classes of psychoactive substances, for example serotonergic psychedelics and entactogens, more work is needed to address the extent to which more subtle differences between substances within the same class (e.g. entactogens) can be measured.

In all psychometric questionnaires including the VAS, AMRS, and 5D-ASC, the subjective effects of MDAI 3.0 mg/kg were slightly

greater than those observed following the 75 mg dose of MDMA but slightly lower than those observed following the 125 mg dose of MDMA (Figures 4–6). Thus, at a dose of 3.0 mg/kg (14 µmol/kg, HCl salt), in this study, MDAI produced pronounced subjective effects comparable with a dose of 125 mg MDMA used in a previous study (corresponding to 1.9 ± 0.2 mg/kg body weight [mean ± SD]; 8.3 µmol/kg HCl salt).[40] The fact that identical psychometric outcome measures were used for capturing the acute subjective MDMA effects suggested that MDAI showed approximately 60% of MDMA's potency in eliciting comparable psychoactive effects.

3.5 | Limitations of the study

There are several important limitations. The MDAI study was small and employed a non-blinded design without a placebo control group. MDMA was administered to another group of subjects and effects of MDMA and MDAI were not directly compared within subjects. Additionally, MDMA was administered in a different setting and in the morning, whereas MDAI was administered in the evening, which could affect subjective and physiological effects. Although the psychometric instruments used were identical in both the MDAI and MDMA study, the tests were administered by different researchers and in a different setting. Similarly, vital sign assessments and the analytical methods used to determine the endocrine parameters were different. Furthermore, it is worth noting that the results presented in the present self-administration study were obtained and interpreted by researchers highly knowledgeable of the physiological and psychological effects of psychoactive substances, which might add an additional layer of constraints when attempting to generalize these findings. However, the use of identical measurements of the subjective mood effects in the MDAI study as used in the MDMA studies allowed for meaningful comparisons with this prototypical empathogenic substance. Larger placebo-controlled studies are warranted to assess the effects of MDAI in more detail.

4 | CONCLUSIONS

The acute subjective effects induced by the NPS 5,6-methylenedioxy-2-aminoindane (MDAI) (3.0 mg/kg, p.o.) were well tolerated and qualitatively comparable with those elicited by racemic MDMA. A preliminary estimation relative to the 125 mg MDMA dose suggested that MDAI might show about 60% of the potency of MDMA. Further placebo-controlled studies are needed to assess the effects in more detail. Currently available in vitro and in vivo data have shown that MDAI is capable of enhancing monoaminergic signaling, suggesting that recreational use of MDAI in less well controlled settings at high doses and/or in combination with other psychostimulant-type substances might increase the risk of adverse effects, similar to what is known about MDMA under such conditions. On the other hand, MDAI might be an interesting alternative to MDMA for use in psychotherapy because experimental data suggest a lower neurotoxicity of MDAI.

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