pharmahuasca: on phenethylamines and potentiation

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I READ WITH INTEREST Alfred Savinelli and John H. Halpern's *Short Communication* "MAOI Contraindications" in the Autumn MAPS BULLETIN [VI(1): 58, 1995], concerning the well-known incompatibility of monoamine oxidase inhibitors (MAOI) and foods containing tyramine and other phenethylamines, and the more recondite contraindication against ingesting MAOI in combination with serotonin-uptake inhibitors like *Prozac.*® A similar warning has been voiced in these pages [MAPS BULLETIN IV(2): 30–32, 1993; IV(4): 58, 1994] and elsewhere[1] by J.C. Callaway, neurochemist, ayahuasca specialist and originator of the *endohuasca* hypothesis (of dream visions involving interaction between endogenous tryptamines and MAOI). I wish to comment on the MAOI/ß-phenethylamine contraindication as it concerns ayahuasca, *anahuasca* (so-called 'ayahuasca analogues') and *pharmahuasca* (anahuasca prepared with pure compounds), and draw attention to a statement made by Savinelli and Halpern, which is certainly misleading, if not outright false.

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Savinelli and Halpern state: "The mechanism of MAOI can be used to potentiate most classes of tryptamines as well as many other classes of drugs." Callaway has also made similar statements: "It is well known that ßCs [ß-carbolines] potentiate the activity of methylated tryptamines..."[2] and "harmala alkaloids can facilitate and potentiate the psychoactivity of additional components [of ayahuasca] through enzyme inhibition."[3] Note the verb *potentiate*, meaning in pharmacology 'to render more potent.' The mechanism of the 'ayahuasca effect' (facilitation of oral activity of DMT by inhibition of the enzyme monoamine oxidase), first proposed by Holmstedt and Lindgren in 1967,[4] has lately been verified by human psychonautic bio-assays[5] and is now widely accepted. Although oral DMT in pharmahuasca is surely more active than taken neat (doses up to 1.0 g inactive in human subjects[6]), since the compound appears *not to be orally active at all* absent MAOI, it would be misleading to characterize this effect as *potentiation*. Moreover, the scant human pharmacological data we have on DMT suggests that the drug is less active orally in *huascas* than by other routes — intravenous or intramuscular injection, or inhaling the vaporized base.[5,6,7,8] A similar correspondence seems to hold for the orally-inactive 5-methoxy-DMT [*O*–methyl bufotenine], orally-active when ingested in pharmahuasca, but weaker than via smoking or injection.[5] This is certainly *not* potentiation!

Moreover, there is experimental evidence that the pharmaceutical MAOI iproniazid (*Marsilid*®) markedly *inhibits* the visionary effects of DMT injected intramuscularly. In seven subjects given intramuscular injections of DMT (two at 0.35–0.55 mg/kg; five at 0.65–0.83 mg/kg), *greatly reduced* psychoactivity was observed when the experiment was repeated two days after having received 100 mg iproniazid daily, for 4 days ("the DMT psychosis... was less pronounced; there were illusions and hallucinations, but

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without colours, or only with a few of them").[9] The author commented that the "high 5-HT [serotonin] level" produced by the MAOI blocked the effect of DMT, thought to owe its psychoactivity to serotonin antagonism — with higher background levels of serotonin, higher doses of DMT would be required to produce equivalent effects absent MAOI. Earlier experiments had established that pretreatment with 'antiserotonin,' a serotonin antagonist, D-lysergic acid butanolamide (UML-491, methysergide, *Sansert,*® *Deseril*®—1-2 mg administered perorally 30–40 minutes prior to DMT injection; or 0.5 mg injected intramuscularly 10 minutes prior) had "a very strong potentiating effect on the experimental dmt–psychosis."[10] That is, it was serotonin antagonism which truly potentiated DMT, while the increased brain serotonin resulting from MAOI pretreatment rather had the opposite effect of DMT–blocker, which would explain our limited human pharmacological data showing DMT weaker orally in *huascas*. Of course, we now know that UML-491 is itself psychoactive and LSD-like, but only in higher doses than employed here — 4.3 mg was said to be equivalent to a nominal 25 mcg dose of LSD.[11] Similarly, it was reported in this Bulletin [*MAPS BULLETIN* V(1): 32, 1994] that "serotonin... receptor blockade [by pindolol or *Visken,*® a 4-hydroxy-indole developed by Sandoz in structure-activity-relationship studies of psilocin] enhanced the psychological effects of DMT." Again, we have seen that MAOI hardly can be said to *potentiate* DMT; if anything, the reverse obtains, with serotonin antagonism/blockade, rather than MAOI–type serotonin enhancement, showing true potentiation of DMT.

What, then of "other classes of drugs"— have we evidence that MAOI can potentiate other visionary drugs? In the case of LSD, emphatically not. The MAOI iso-carboxazide (Marplan®) was used as pretreatment to oral doses of 40 and 75 mcg LSD in 4 human subjects, all of whom "volunteered the information that, following Marplan pretreatment, the experiences produced by LSD-25 were either very markedly attenuated or did not develop at all... all four subjects were emphatic... that, following LSD-25 plus Marplan pretreatment, they did not experience anything in any way similar to the experiences produced by LSD-25 without Marplan pretreatment" (each experimental subject had experienced both doses of LSD neat, and both after 2 weeks of 30 mg/day isocarboxazide, and after 5 weeks of this MAOI at 30 mg/day).[12] I might note parenthetically that Marplan, 30 mg/day, was shown in a single human bioassay to render DMT active orally.[5] It was reported in these pages that interviews conducted as part of an NIMH study showed a "decrease in response to LSD... in those people who had been taking an MAO inhibitor [for medicinal purposes]" [MAPS BULLETIN V(1): 9, 1994]. We thus have both experimental and anecdotal evidence that MAOI, far from potentiating LSD, rather seem to exert an effect parallel to that of DMT -blocker, serving also as LSD-blockers!

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TO BE SURE, I have heard considerable anecdotal evidence, to the effect that pre-treatment by Syrian rue seeds, ß-carboline-rich seeds of *Peganum harmala L.* used in anahuasca,[5] can potentiate the effects of psilocybian mushrooms, pursuant to this general notion of ß-carbolines as all-purpose potentiators of visionary drugs. However, nobody has proffered hard evidence of this, even with the most rudimentary controls. All the anecdotal evidence I have heard concerns vague bioassays involving psilocybian mushrooms as the psilocybin source, sometimes not even weighed doses, but counted, by pairs! Since potency of psilocybian mushrooms is notoriously variable, even in commercially-cultivated *Psilocybe cubensis* (Earle) Singer (in commercial-style Mason jar cultures, there was up to a four-fold variation in potency of individual mushrooms from a given jar,[13] even up to nearly three-fold variation in psilocybin content between caps and stems of the same mushroom[14]). Given this gross variation in psilocybin potency, even of cultivated mushrooms, and the fact that, as we have seen, MAOI weaken, rather than potentiate, DMT and LSD, we will need controlled human bioassays with pure ß-carbolines and psilocybin in pharmahuasca capsules to establish whether or not MAOI can truly potentiate psilocybin. Vague reports to the effect that "when I took three pairs (or three grams) of mushrooms after swallowing a handful of ground-up Syrian rue seeds..." are worthless for the purpose of establishing synergy or antagonism. Nevertheless, inasmuch as so many people have avowed that Syrian rue seeds potentiate psilocybian mushrooms, there must be some truth to this. I am not claiming this is not true, only that we have no solid proof of this. Since data on related visionary tryptamines DMT and LSD suggest conventional wisdom on this point is wrong, any potentiation of psilocybin by MAOI would be an anomaly, hardly expected — certainly not to be taken for granted.

All this begs the question of the primary locus of MAO inhibition in the ayahuasca effect. The limited data suggest a neurochemical effect of MAO inhibition is as DMT- and LSD-blocker — when MAOI are taken chronically, as used medicinally, so that therapeutic, high serotonin levels are achieved in the brain, both the effects of intramuscularly-injected DMT and oral LSD are inhibited.[9,12] Conversely, oral or intramuscularly-injected

methysergide, having the opposite neurochemical effect of antagonizing serotonin, was shown to exert a "very strong potentiating effect" on intramuscularly-injected DMT,[10] while pindolol, which analogously blocks serotonin receptors "enhanced the psychological effects of DMT." This is consistent with the hypothesis of DMT psychoactivity as a result of serotonin antagonism — MAOI, which elevate brain serotonin, inhibit the DMT effect, and the serotonin antagonist methysergide and serotonin receptor blocker pindolol enhance it. It thus follows that the ayahuasca effect is due to MAO inhibition in the digestive system or blood stream, protecting DMT from metabolism en route to the brain, where the MAOI paradoxically attenuate the DMT effect. I found that *Marplan* (which "very markedly attenuated" LSD activity when taken orally 30 mg/day over 2 or 5 weeks), ingested in 3, 10 mg doses on a single day, activated 30 mg DMT taken orally an hour after the third dose.[5] It seems that in this case, *Marplan* sufficiently inhibited digestive MAO as to allow absorption of the DMT; all before sufficiently high brain serotonin levels could inhibit its effect. I questioned Deborah Mash at the UDV meeting in Rio in November 1995, whether her preliminary data on human pharmacology shed light on this problem. Her response was that the primary site of MAO inhibition in ayahuasca seemed to be peripheral, i.e. in the digestive system or blood stream.

This brings me to my second comment on Savinelli and Halpern's article — the MAOI/ß-phenethylamine contraindication. While these authors and Callaway are quite right to caution would-be experimenters regarding the dangers of ingesting foods rich in tyramine (4-OH-ß-phenethylamine), should they be under medical treatment involving chronic, daily ingestion of MAOI like *Marplan*, I argued that such strictures do not necessarily apply to users of *huascas* based on ß-carbolines as MAOI.[5] There are gross differences in dose regimen, toxicity and pharmacodynamics of ß-carbolines, as opposed to medicinal MAOI like *Marplan* — the latter are potent, generally irreversible inhibitors (that is, they bind irreversibly to MAO molecules, thus destroying them) which are ingested daily over lengthy periods, taking from a few days to a few months to exert their maximum effect, which may persist for a like time even after cessation of daily ingestion. In other words, their use involves a chronic, full-scale alteration of biochemistry, not just of the serotonin system. In the case of the ß-carbolines, these are reversible MAOI (that is, they compete with normal substrates for active sites on the enzyme molecules, but do not bind to them permanently) taken in single doses, with a transient effect, estimated by Callaway to last only "for several hours" [*MAPS BULLETIN* IV(2): 31, 1993]. I have personally tempted fate, and ingested cheese, beer, chocolate, caffeine, nuts, dried fruit, etc. in the afterglows of my *pharmahuasca* and *anahuasca* experiences, with no ill effects whatever.[5] While I am in complete agreement with Callaway's warning, that "MAO inhibitors, in general, are not safe drugs to play around with" [*MAPS BULLETIN* IV (4): 58, 1994], we in fact have no evidence that ß-phenethylamines are rendered toxic by combination with single doses of ß-carbolines, such as are employed in *huascas*.

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Moreover, there is circumstantial evidence for traditional use of ayahuasca containing mescaline and/or other ß-phenethylamines in Amazonian Peru. One of the most complete scientific studies of ayahuasca yet conducted reported the use by Peruvian Indians of a cultivated *Opuntia* species, called *tchai* in Sharanahua, as an ayahuasca admixture, and said to be "very strong." Another cactus, a species of *Epiphyllum*, known as *pokere* in Sharanahua and *wamapanako* in Culina, was likewise added to ayahuasca.[15] A Shipibo informant recently stated that *tchai* was no longer employed in ayahuasca, the resulting brew becoming "too intense."[16] We have no phytochemical data on these cacti, but several species of *Opuntia* are known to contain low levels of mescaline,[17] and preliminary human bioassays suggest that the ß-carboline harmaline might in fact potentiate mescaline — low doses of 60 and 100 mg mescaline hydrochloride, corresponding to 51 and 86 mg base or 0.78 and 1.32 mg/kg respectively, were decidedly psychoactive. The combination of mescaline or mescaline-containing cacti with ß-carbolines has been dubbed *peyohuasca*.[5,18]

It is therefore obvious that Savinelli and Halpern's statement that "MAOI can be used to potentiate most classes of tryptamines as well as many other classes of drugs" is dubious — seemingly false in the case of DMT and 5-methoxy-DMT, likewise in the case of LSD; possible but unproven in the case of psilocybin, and seemingly true in the case of mescaline. We must ever be cautious not to go beyond our (in this case scant) evidence, and in light of Callaway's sagacious admonishment about "playing around with" MAOI, careful not to encourage the evident fad in Syrian rue seed use as a purported, multi-purpose, panpotentiator of visionary drugs — one 'basement shaman' has even combined Syrian rue seeds with Salvia divinorum (the active principle of which, salvinorin A, is not even an amine![19]), to yield Salvia ayahuasca.[20] It seems the warnings of incompatibility of ß-phenethylamines

with ß-carbolines are premature if not exaggerated, and we must bear in mind the 'boy who cried wolf syndrome,' so as not to vitiate the warnings about the so-called 'serotonin syndrome' resulting from combining MAOI with serotonin-uptake inhibitors like the popular Prozac, whose use likewise has achieved the status of a fad. Deaths have resulted from this combination, although again, these involved the pharmaceutical MAOI moclobemide, not single doses of ß-carbolines; combined with citalopram and clomipramine, not fluoxetine or Prozac. However, given the facts that moclobemide is a reversible MAOI, and that already numerous deaths have been attributed to this 'serotonin syndrome,' not to forget the overblown popularity of Prozac (today's 'miracle drug,' tomorrow's drug-abuse scourge), this warning is appropriate.

IN CONCLUSION, I wish to add my own warning to psychonauts and 'basement shamans' who experiment with pharmahuasca and anahuasca. It has come to my attention that some swallow capsules of Syrian rue seeds rather than make aqueous infusions, or swallow juice of Phalaris or root bark of Mimosa tenuiflora (Willd.) Poir., all to avoid tasting the bitter medicine. However, making aqueous infusions effects a crude separation, leaving behind non-water-soluble constituents, potentially toxic. Existence of traditional use of aqueous infusions of M. tenuiflora roots, as vinho da jurema, does not constitute proof that it is safe to swallow the roots or their bark themselves, and one colleague experienced toxicity from so ingesting capsules of ground M. tenuiflora root bark as anahuasca, whereas a prior experiment with an aqueous infusion of the same root bark provoked no such toxicity. This toxicity may have been due to the chalcones kukulkanins A and B found in bark of M. tenuiflora, and which are lipid-soluble,[21] and would not appreciably be extracted into water. Similarly, apart from containing high amounts of ß-carboline alkaloids, Syrian rue seeds also contain significant levels of the uterotonic quinazoline alkaloids vasicine (peganine) and vasicinone, accounting for ethnomedicinal use of these seeds as an abortifacient.[5,17,22] Since these alkaloids are much less soluble in water than are the ß-carbolines, once again making an aqueous infusion will effect a separation, leaving the bulk of the quinazoline alkaloids behind in the seed residue, amounting to lower toxicity, especially significant for women, particularly if they are pregnant. Clearly, in their zeal to avoid tasting their bitter medicine, anahuascanauts are playing with fire, exposing themselves to unnecessary risks, ingesting preparations lacking some traditional track-record for human safety. All to avoid tasting the bitter draught... but some regard withstanding this bitterness as a rite of passage... as James Joyce said,[23] "no roses without thorns"... but Joyce was referring to women, not to drugs! •

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