Editorial

Some key principles in psychopharmacology: Editorial[abc]

Editorial

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Vernon M Neppe,[d1,2] Jeffrey Mishlove PhD[ef]

[1]Director, Pacific Neuropsychiatric Institute and Exceptional Creative Achievement Organization, USA

[2]Department of Neurology and Psychiatry, St. Louis University, USA

Correspondence: Vernon M Neppe, Director, Pacific Neuropsychiatric Institute and Exceptional Creative Achievement Organization, Seattle, Washington, USA, Tel 206-527-6289, Email psyche@pni.org

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JM: Today we're going to look at the uses and abuses of psychiatric medication. With me is Neuropsychiatrist Dr. Vernon Neppe who is the author of *Reality Begins with Consciousness*[22] a theoretical book about consciousness and science co-authored with physicist Edward Close. Dr. Neppe has also written *Cry the Beloved Mind*,[4] a book about his use of psychiatric medications and also the uses of *Innovative Psychopharmacotherapy*.[10] Vernon you've been prescribing psychiatric medications and related medications now for many decades and in fact you're one of the leading proponents of the neuropsychiatric medications.

VN: Well it depends how you mean 'leading proponents'. I would say I've tried to use psychopharmacological treatments appropriately, so that doesn't mean leading proponents because there are times when I take people off as much medication as I put them on medications.

JM: I really didn't mean proponent in terms of advocacy, I meant it more in terms of your knowledge.

VN: That might be so: I was fortunate enough to have been listed for some reason by the Collegium Internationale Neuropharmacologicum, which is the leading group in psychopharmacology in the world--as one of the 'Leading Psychopharmacologists of the 20th Century'.[26]

JM: And, in fact, you were one of the pioneers in off-label use of anti-seizure medications.[27–29]

VN: Yes, I pioneered the use of anticonvulsants in patients with psychiatric disorders but specifically we were looking at patients who had certain kinds of unusual symptomatology[30–32] which turned out to be linked up with the temporal lobe of the brain.[31–35]That was one of the findings that I am pleased has helped possibly millions. I had already been working with anticonvulsants in the early eighties and realized, it, like several other anticonvulsants had great versatility in putting out abnormal electrical fires in the brain, including those manifesting as some anger explosions,[34] and profound rapid mood fluctuations.[36–39] These were also sometimes mobilized by recreational drug use and I described a phenomenon I called 'chindling' which was effectively 'chemical induced kindling'.[40] Somehow, the term

[a]This is adapted (with references and revised slightly for the written word) based on a YouTube entitled *Psychotropic Medications with Vernon Neppe* at *Psychotropic Medications with Vernon Neppe* https://www.youtube.com/watch?v=1Xj5vEyqUlo[1]

Along with some two dozen other YouTubes by Dr. Vernon Neppe, it can be found at http://vernonneppe.org/presents/ Many of these are based on interviews with a Psychologist, Dr. Jeffrey Mishlove PhD. Dr. Neppe regards Jeff's skill at interviewing and remarkable knowledge throughout his unique series, New Thinking Allowed is a great gift to mankind not only for now but for the future. For a complete, updated list with links to all the New Thinking Allowed videos--as well as many other opportunities to engage with the New Thinking Allowed video channel--please visit the New Thinking Allowed Foundation at http://www.newthinkingallowed.org. Dr. Neppe greatly acknowledges Dr. Mishlove's permission for this article editorial.

[b]The dialogic style along with Science through Fiction ('sciction')[2,3] was developed by Dr. Vernon Neppe in his book *Cry the Beloved Mind: A Voyage of Hope*[4] along with his play Quakes.[5]

JM is Dr. Jeffrey Mishlove; VN is Dr. Vernon Neppe.

[c]The original description for the YouTube read (referencing is added) (this is largely Dr. Mishlove's wording).

"Vernon Neppe, MD, PhD, FRSSAf, is a neuropsychiatrist and head of the Pacific Neuropsychiatric Institute in Seattle. He is a Distinguished Fellow of the American Psychiatric Association, and recipient of the Whiting Memorial Award.[6–9] He is author of two major psychopharmacology books, *Cry the Beloved Mind: A Voyage of Hope*[4] and *Innovative Psychopharmacotherapy*[10] (www.brainvoyage.com), and many other books including (the original classic *The Psychology of Déjà Vu*: Have I been here before?),[11] *Déjà Vu Revisited,*[12] *Déjà Vu: A Second Look,*[13] *Déjà Vu: Glossary and Library*.[14] He was chosen (in 2004) as one of the *'Leading Psychopharmacologists of the Twentieth Century'*[15] by the Collegium Internationale Neuropharmacologicum. He also led the first ever USA and International Delegation in Psychopharmacology and Neuropsychiatry (to China).[16]

Dr. Neppe has amplified many of his concepts in three of the websites linked with his work. His books are amplified on www.Brainvoyage.com; www.VernonNeppe.org is his gateway and includes more information on the Neppe-Close model of the Triadic Distinction Vortical Paradigm (TDVP) and some of the key publications are on www.pni.org. Together with Dr. Edward Close, he pioneered the new discipline of what they call Dimensional Biopsychophysics'.[17–19] He is author, with physicist and mathematician, Edward Close PhD, PE, of Reality Begins with Consciousness: A Paradigm Shift that Works.[20–22] His professional publications number over 700.

Here, Dr. Neppe describes the many factors requisite for proper prescription and monitoring of psychiatric medications. He maintains that these drugs can be remarkably effective, and even life-saving, when used properly. However, there are instances in which physicians do not adequately take into account such factors as body sensitivity, multiple diagnoses, nutraceutical interactions, therapeutic windows, dose frequency, dosing and side-effects. There are also issues related to the proper use of generic drugs. Legislation may be required to address some issues." (This YouTube was recorded on May 1, 2018).

[d]Vernon M Neppe MD, PhD, DFAPA, FRSSAf, MMed, DPM, FFPsych *Pacific Neuropsychiatric Institute, Seattle, and* Exceptional Creative Achievement Organization, USA ©*Corresponding author:* Vernon M Neppe, questions@pni.org.

[e]New Thinking Allowed host, Jeffrey Mishlove, PhD, is author of *The Roots of Consciousness,*[23] *Psi Development Systems,*[24] *and The PK Man.*[25] Between 1986 and 2002 he hosted and co-produced the original Thinking Allowed public television series. He is also past-president of the non-profit Intuition Network, an organization dedicated to creating a world in which all people are encouraged to cultivate and apply their inner, intuitive abilities."

[f]Our grateful thanks (alphabetically) to Anne Marie Arvidson, Ed Close, Joe Slabaugh, Erich Von Abele, Suzan Wilson, and the 1800 listeners to the original YouTube!

'chindling' never caught on, although in my experience it's more pertinent than 'kindling'[41] where over time, even though repeated stimuli that should be too low, induce seizures or what might be the equivalents in the brain.[42]

JM: And you discovered another important treatment, did you not?

VN: Yes, another major milestone was when I found a treatment for a (technically previously) incurable condition called tardive dyskinesia.[43] This seems to be still so today--I discovered this off-label use of high-dose buspirone in 1989:[43–45] When using it, the results are so dramatic that there would be an ethical dilemma as to whether one could even use it in a double-blind placebo controlled study: It's not like 60% improve compared with placebo, but, in our experience, almost every patient who tolerates doses of say 120mg to 180mg per day, improves dramatically. I suppose this is another area that I'm most well known for. However, there are other areas in which I described the innovative but effective use of the more usual doses of buspirone, too.

JM: Like?

VN: I've also used buspirone in much lower doses clinically in novel ways in aggression,[46] attention deficit disorder[47] and suicide prophylaxis and assisting maintaining the efficacy of Selective Serotonin Reuptake Inhibitors antidepressant-drugs and taught about these areas in my lectures.[4,48]

JM: Well I have had the privilege of over the years doing interviews with a number of the I guess you call them the anti-psychiatry advocates people who would say that psychiatric conditions are over diagnosed and psychiatric medications are over prescribed and that in general the millions of people in our society who are taking tranquilizers and antipsychotic medications of various kinds are doing themselves more harm than good.

VN: I suspect you want to ask me a question in that regard--is that true?

JM: What is your opinion about that?

VN: My opinion is that there is the correct way to prescribe and many incorrect ways to prescribe and a lot of psychiatric prescriptions are not good not because the medications are wrong but because they are used inappropriately--they are used under the wrong circumstances, sometimes the diagnoses are wrong, and diagnosis in psychiatry is just awful from a labeling point of view. The second component is they are sometimes used in an imprecise dose, for the incorrect indications, for the wrong duration of time, for the inexact frequency--like some medications need to be prescribed twice a day and might be prescribed only once a day, and the whole advent of *generic medications* has changed the whole ballgame. And these are components where patients don't even realize it and then they take supplements and they also have combinations of medications: Sometimes those combinations are used to treat the side- effects of other medications. So in relation to your comments I can imagine your having interviewed quite legitimately several people who might say well these psychotropic medications do more harm than good.

JM: I've also talked to people who have been patients who say these drugs saved my life.

VN: Right: the point about it is if you had to look at it on a balance, they can do more harm than good, but the great, great majority of these medications are wonderful medications when used appropriately at the right time under the right circumstances with the right patient for the right diagnosis for the right durations and they are wonderful and indeed would save a lot of lives.

JM: Well I know for example it seems as if in the last several decades there's been almost an epidemic of ADHD hyperactivity diagnosed amongst young children, and then they get prescribed a drug called Ritalin very commonly used these days which to my understanding it's *almost* in the same family as methedrine or Dexedrine--it's an amphetamine.

VN: Well I used to lecture very extensively on *attention deficit hyperactivity disorder* around the country and I used to say it's the most over diagnosed of conditions it's the most under diagnosed of conditions and it's the most misdiagnosed. And so you quite right there are many, many kids who are given drugs such as methylphenidate which is Ritalin (not an amphetamine), or one of the amphetamine drugs and that these are inappropriate and not based on appropriate evaluation. And on the other hand there are children and now adults--because we realize that you're dealing with an adult attention deficit disorder condition as well--where it is life-saving and these drugs totally change people's lives.[4]

JM: So could amphetamines be particularly harmful?

VN: Possibly, yes, I'm afraid. The amphetamine group of drugs because the amphetamines are sometimes—and this is with great respect to my colleagues, I mean no insults, and not to deprecate them in any ways, but let me just say that these drugs are sometimes prescribed under situations that I would not prescribe them, and that particularly, I recall, amphetamines we find were banned or have been banned in several of the English-speaking countries at times ranging through from South Africa where I came from to Great Britain to Australia to India to Israel to even Canada at times.

JM: Does the FDA not exert control?

VN: Let me say this: Despite the very careful regulatory body of the Federal Drug Administration (FDA), we find amphetamines being prescribed by primary care physicians and completely wrongly: And sometimes these can induce psychotic phenomena in a small population of people to the extent that the psychiatric biographer of Adolf Hitler, Dr. Leonard Heston,[49] had written about the fact that Hitler became a paranoid psychotic as a consequence of the amphetamines he was receiving and he would take barbiturates at night to sleep; and there are stories that a lot of the German army were on these drugs and one wonders about how these would have changed their mental state. As an aside, some would refer to the 'model psychosis' which could be induced by a variant of amphetamines in the early 1950s.[50–52]

I sympathize with people who are busy saying but these drugs are very harmful; you know the first rule in medicine is "first not to poison" from the Latin "*primum non nocere*". However, there's a lot of poisoning that goes on, but when used properly, medications are also usually far the most valuable treatment we have for many conditions.

JM: Well let's talk about your approach to drug prescription. I know in your book *Cry the Beloved Mind*[4] you talk about how you have to so very carefully balance the dosage.

VN: Yes, and this began in fact with my book *Innovative Psychopharmacotherapy,*[10] where I created certain rules. For example you give a person an *antipsychotic* drug but they are not biologically psychotic, they're going to get side effects[53] and their side effects might be short term or long term side effects.

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I'm not saying if people receive antipsychotics and get side effects it is necessarily they're getting the wrong prescription but you've got to open your eyes and you've got to realize that if people cannot so to say 'tolerate average doses of antipsychotic' it's probably because biologically they are not psychotic; and of course in *Cry the Beloved Mind*,[4] I emphasize the fact that the first thing you've got to do is you've got to examine your patient and know what their condition is like and know the diagnosis.

JM: So what would you say are the key principles?

VN: It's a question, inter alia, of *prescribing for the appropriate patient, applying the correct diagnosis or cluster of symptoms, with the treated for the right time and applying criteria such as frequency of dosing, drug interactions, balance of treatment with side-effects, individualizing treatment, support and their attitudes. It also implies knowing the medical, psychiatric and pharmacological history, family history and dynamics, evaluation of other factors such as possible reasons for non-responsiveness, and individualization.*[54,55] *I like to know the positive factors that can be applied, as well as the negative. And I regard a systems approach as important: the ethicospirituobiopsychofamiliosocioethnicocultural approach!* [56]

JM: How does this apply in practice?

There is no reason why medication management and the various therapies should be done separately by the same practitioners. On the other hand, practitioners should be qualified to prescribe medications. Psychopharmacology is a complex skill requiring medical training. I know that shortages do not necessarily allow for ideal situations: Those geographical areas that allow prescriptive privileges to psychologists who are not trained in Medicine might be compromising an essential part of the medical care of the patient: I say this controversially, realizing that we could devote a whole book to this topics and there are arguments both ways, but the issue needs to be raised.

JM: And this you recognize as simplistic?

Yes. It might not even be that the psychiatric diagnosis is the most pertinent feature. It. certainly might be a psychopharmacological one, looking at how they've responded and how members of family have responded and going from there. There is also now a whole genetic component in which we can recognize the specific biological differences at both brain and liver levels and this may be deciding factors for choice of the appropriate agent.

And it might be that you've got to investigate these people. I cannot tell you how many patients I see with depression who cannot get better because simply their thyroid has not been properly managed[57,58] or their vitamin B12[59–63] or even their vitamin D levels;[59,64,65] and so this introduces a whole new ballgame of nutritional supplements that are appropriately used.

JM: Most doctors to my knowledge avoid any consideration of *nutritional supplements*.

VN: They have virtually no training in it – it's a rarity--and this is universal around the world. And I sometimes say to my patients I almost feel like a naturopath because I'm busy giving them a variety of different nutritional supplements if they need it (but only if they need it) and knowing the problems with it.

JM: A bottom line would be?

VN: The bottom line is this: A doctor can try very hard to treat a patient with for example, resistant depression. But if he does not treat the underlying problem be it diabetes, or hypothyroidism (with a TSH level of 2 or 2.5 at most mIU/L),[57,58] or Vitamin B12 deficiency (maybe at least 700 or 800 pg/ml if neuropsychiatric manifestations; many laboratories will quote 180 or 240 0r 300 but that is clinically much too low in the psychiatric populations).[59–63] Also, Vitamin D deficiency: for me these are levels far higher than expected e.g., 60 or 70 if patients are symptomatic; many laboratories will quote 20 or 30nmol/[66] or but that appears clinically much too low in the psychiatric populations,[59,64,65] that refractory patient is going remain so.[4] And the same applies to low magnesium and adequate calcium requiring well-absorbed parts to be higher.[67–70]

JM: And what of the role of supplements?

VN: I draw attention to one of the comments that I make my book in *Cry the Beloved Mind: A Voyage of Hope*[4] written in a dialogic style, it's called 'sciction'--science through fiction (they didn't know where to put it in the bookstores, do you put it under fiction or nonfiction?); but be that as it may.

One patient dialogue is: "*But doctor this cannot do any harm, these are natural supplements!"* And the doctor says *"Snake venom is also natural."*[4] And this is the whole point, so you've got to know that there is poisoning but overall if people are trained in psychopharmacology they know what they're doing, but on the other hand, it doesn't mean to say that they should be ignoring that human-patient interaction because the role of--let us call it 'placebo' although it's not really placebo--it's the role of the relationship with the patient, which is something that is uppermost and something that is so, so important.

JM: I would think that, at some level, the art of prescribing these drugs has to go beyond the known science because when you're dealing with a person's diet, a person's family history, a person's metabolism, and then the various dosages of different drugs that they may be having in combinations of drugs, the scientific literature never gets that specific.

VN: Right, it doesn't. You use that word 'art' and you've also used the word 'scientific'--and it's both: *The practice of medicine is a science and it's an art*. But never forget that the practice of medicine is based on an absolutely bizarre assumption. In order for drugs to be approved for a particular indication--so for example in the United States--there has got to be two separate double-blind studies showing statistical significance versus placebo with that drug. Now there's a problem. First of all, a lot of medications are so well-established so it is almost unethical to say "Look even though we know this drug works, we're going to give you and you won't know which one because it's double-blind – and I won't know either--you'll either be getting placebo (a sugar pill, so to say) or you'll be getting active drug."

And sometimes it's completely unethical and I've seen a friend of mine a medical colleague whose son developed cancer and there was a very, very good new drug out there for him but the trouble was they were busy doing their double-blind studies and his son had a 50% chance of getting placebo or active drug which would help.

JM: On the good side though, the placebos also seem to have a positive effect; very often one of the strongest effects in all of medicine, I'm told.

VN: Yes this is true but under certain circumstances when somebody is known to be potentially going to die of that cancer within a year or two and there's a new drug that is out there that might

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cure that cancer--are you going to say well let's go into the *double-blind study*[71–73] and hope? Well, this particular person was able to persuade one of his colleagues to prescribe this drug or make sure the person was in the right group, but the point that I'm making is something a little different here and we've alluded to this in a previous discussion: If I'm giving you an antibiotic you want that antibiotic to work particularly if I've done a throat swab for example and I know the bug that is involved. You don't want it to work in 52% of cases even though a placebo that is prescribed might work in 48% of cases--and yet those double-blind studies are based on this. You want the antibiotic to work in 98% of cases ideally.

And this is where the difference comes in where we have the fuss of what is falsifiable and in medicine you're doing these studies and trying to prove that it is *better than placebo* based on statistics versus what is feasible. And also you want to take into account another balance: I said *the right dose in the right time and the right circumstances in the right frequency--and the whole game of generics is a whole new ballgame*. You also want to have what is feasible: You don't want to have loads of side effects and I've seen patients getting many, many side effects on particular medications.

JM: There is also the issue of withdrawal symptoms.

VN: Yeah, and that's terribly important and you see it all over the place. There are fashions in medicine and in society and maybe in politics as well. I cannot say that I'm very fond of marijuana; now marijuana in certain circumstances under certain controls using the correct dose of the appropriate chemical subtype at the proper time for the right symptoms might have certain potential benefits.

But on the other hand, I've seen patients develop *amotivation* syndromes and this is common.[74,75] They lack motivation and they lack drive and there is a certain subpopulation of people who develop frank psychotic conditions.[74] People sometimes say maybe it'll mobilize schizophrenia, but you know strangely enough based on my research and known descriptions, it's a different condition. I know this because of my original work with anticonvulsants in psychiatry.[31,32,34,35,76,77] Some of these people were resistant; I even would see them in a mental hospital setting, they would be labeled psychotic maybe sometimes schizophrenic or something but they're not schizophrenic and they were receiving the wrong drugs--the antipsychotics--in the wrong dosage under the wrong circumstances because of the wrong diagnosis. There were drug-induced mobilized conditions and they needed particular drugs like adjunct anticonvulsants. Yet, with respect, our research[74,75] has been largely ignored, possibly because it's not fashionable to address the dangers of marijuana.

JM: So anticonvulsants can measure response to underlying conditions?

VN: Sometimes:[31] It might relate to putting out the underlying 'fires in the brain' irrespective of whether the patient has been regarded as having a seizure disorder.[31,32,34,35,76,77] The anticonvulsant I researched at the time was one called *carbamazepine* (or Tegretol). So I'm one day giving a lecture to a group and the chairman stands up and says *"We all know Dr. Neppe, he's a man of great' integretol'"*.

But the point about this you've got to know what you're doing and psychopharmacology is a science--and don't think it's just a science in the United States: I had the good fortune to lead the first international delegation in neuropsychiatry and psychopharmacology and this was to China. I was amazed at two things: the one was they were going through the same prescription dilemmas as we discovered in the United States, but strangely enough they were more open to other forms of medicine.

JM: Like?

VN: There was an acupuncture unit right there in this so-called Western Hospital. There would be a herbal medicine department with a whole string of different herbs—most of which I confess when you spoke to them they weren't quite sure what the pharmacological components were—and they would mix it all, which I don't think is particularly good medicine because it can produce side effects.

But I was intrigued that the same kinds of critiques I would have on our medications here they would have there. So for example there's a group of medications called the 'selective serotonin reuptake inhibitors'—the *SSRIs*—they are prescribed like water in terms of depression. Now let me just mention, I may be wrong, everyone else might be right, but that is the last subpopulation of antidepressants I will prescribe unless I know the patient has specifically pharmacologically responded to it or they've been on that drug and are doing well or there's a family history component--because I sometimes quip, *"Wow! In neuropsychiatry we see patients with neurologic and psychiatric conditions and I can earn my living from the SSRIs!"* These patients come along and many report headaches requiring additional treatment, or they have insomnia— and when they have sleep disturbance you prescribe something or they've already had something prescribed for their sleep or they come along and the drug stops working.

Or the big joke--and this is just a joke, don't take it too seriously--nobody would ever measure sexual dysfunction because then you've got to report it. When they started suddenly reporting sexual dysfunction with these SSRIs the joke became: *"Well you know 70% of patients have sexual problems on that particular SSRI and the other 30% are lying!"* Of course, that's an exaggeration: But the point about it is it gives a little bit of a perspective: there are far, far safer drugs. Why? Because you're over blowing the serotonin receptor with these drugs[4]—they should have started at maybe one-tenth the kind of dose. So even when drugs are marketed--and again I'm expressing an opinion— I'm not critiquing people who do these things they probably know far more than me but I'm just basing it on my experience—these drugs are far overused, just like you mentioned methylphenidate: overused, underused, misused and misdiagnosed. And then you find all these people coming in with refractory depressions when people have missed the underlying physical conditions.

JM: Let me ask you this question because I suspect amongst our viewers there will be many people who are on these drugs, who are considering the use of such drugs, because I think a high percentage of the population is prescribed to these drugs, I'm going to guess maybe 30%.

VN: Yeah because you find that even years ago, you remember the old but still famous *'Srole 1954 Midtown Manhattan study'*:[78,79,80] it could be as much as 50% of people have some kinds of psychopathology and some very often it's anxiety or depression or insomnia and the two might go together.

JM: But if I'm a patient *how can I be sure that my doctor is doing everything necessary to monitor my use of these drugs?*

VN: You know it's really difficult to answer here because I'll get this from our patients all the time, because I am, if you want a super-

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specialist so I'm used as a consultant, and invariably my patients have psychiatric and neurological conditions.

And they ask: *"is Doctor Smith good?"* I say I don't know, I've never been to Dr. Smith. Because very often it's word of mouth by the patients who are letting other patients know, but sometimes they have no insight because it's that doctor/patient relationship and Dr. Smith might be very, very skilled at that relationship and very good but it doesn't mean to say that Dr. Smith knows what to prescribe. Obviously if you see psychiatric patients, it would be nice for them to have psychiatrists and not primary care physicians for their mental health. I'm lucky: One of the hats I wear is as a Distinguished Fellow of the American Psychiatric Association—another good fortune component of me—but the point about it is, even if you looked at somebody who was a distinguished fellow it doesn't mean to say that Dr. Smith who is a very caring doctor and who monitors his patients carefully is any worse. He might not be, and if I had to advise you're going to have to go to somebody where you form a decent relationship where you trust your doctor and where your doctor is busy monitoring.

JM: Trust and follow-up: Good measures?

VN: Yes. If I put a patient onto a new medication, I will always follow-up early: if I can say I'm prescribing it on Thursday, I want you to phone me, let me know if you have any problems, any side-effects, anytime I want to know these things--and I want you in any event, say on Monday, to give us a call and tell us how you're doing.

I have three kinds of patients I treat: I treat humans and in my practice that's about 80% of patients; and I treat two other kinds of patients: you're supposed to ask.

JM: What are you, a veterinarian?

VN: I treat metaphorical squirrels about 10 percent squirrels and elephants--about 10 percent. Now you see this is the problem: the problem is let's imagine that the patient comes along, now the standard dose is 100 milligrams daily, so I take a pharmacological history and maybe I'm Dr. Smith and I don't bother, "*Oh you've got some depression we'll give you this drug and I'll give 100 milligrams".* But 10 percent of my patients are squirrels, they're absolutely 'zonked' out of their mind by their 100 milligrams. Another 10% are metaphorical elephants--and I've tried to find an alternative term for 'elephants'—nobody minds being a squirrel!

JM: You're not talking about their body type, you're talking more about their sensitivity.

VN: Exactly. I'm talking about the metabolism and particularly the actions of these drugs at the brain level--I'm talking about that sensitivity. And so I prescribe for a 'human elephant', I might need to give 800 milligrams of that drug for any elephant and I might end up giving 10 milligrams for 'human squirrels"--and sometimes I have 'baby squirrel humans' and they even get 5 milligrams--and so this is where the component comes in. We have to individualize dosage sometimes—*not one dose treats all.* Has the doctor taken an adequate pharmacological history? What other drugs have they received? What happened when they have? And when you go into this you suddenly discover, yes, in the general population of people, it's not 80/10/10. I've got this super specialized population, I'd say 90% are human, 5% are squirrels, 5% are elephants.

But imagine I cannot tell you how many poor squirrels I've seen who are told *"Oh it's all psychological (or, you're just being a hypochondriac)"*--and the patient knows it's genuine and they stop taking their medication.

Alternatively, the elephants tell their doctors *"But this doesn't work!"*--so they change them to another medication when in fact they ought to be titrating upwards.

JM: So this is another reason to know which doctor to go to?

VN: Realistically, there are not many physicians who will measure exact responsiveness. But, certainly, one of the reasons, one of the aspects that you have to know is: Is that doctor carefully monitoring? Is the doctor carefully monitoring side effects? Has the doctor discussed with the patient and has the doctor discussed or asked the pharmacist to give a package insert? And what kind of pharmacy are they going to? Those are little components.

JM: In other words if I were to summarize, you want a doctor who is going to take a very detailed history and who is going to monitor you carefully to check on side-effects.

VN: And who's going to review whether there are they any other extraneous problems, like vitamin B12 deficiency,[62,63] hypothyroidism,[57,58] diabetes,[81] so-called MTHFR homozygous—a common disorder of folate metabolism— that you've got to treat.[82,83]We must treat the whole patient. But there is a new problem.

JM: And what would that be?

VN: The little game called *'generic substitution'*.[59,64,65,84–86] And this is not actually a little game, it's a major, major game.

JM: Yeah, because as a naive consumer, I assume the generic substitutions are equivalent to the brand name.

VN: And you'll get half the pharmacists telling you this and you'll get the medical insurance telling you that because they think they can save money. Well there are problems. First of all, with some of the generics, they're not even close to equivalent in terms of the fact that there is a critical index. So imagine that one is taking a heart medication and instead of taking a 100 milligrams of the brand-name you're taking 85 of the generic. And this might fit--you just might die in between because your critical index component is very, very restricted. Maybe you should be taking between 95 and 105 milligrams, and generally the FDA does not worry about critical index drugs which are particularly heart drugs and drugs for seizures for example, and for bleeding disorders: Those are three important groups of critical index drugs.

The second one is one that few seem to know about something called *the 80 —125 rule*.[4,84–86]

JM: No, I've never heard of that rule.

VN: Well you see, *80 —125* means that your generic drug will be approved as equivalent if roughly about 90% fit the statistic of being equivalent to 80% to 125% of the actual branded drug. We're talking general statistics, so more accurately we can draw graphs and say *"Wait a minute, you're talking area under the curve"*: That is correct. But, in effect, if there are 100 milligrams of branded drug, when the generic is approved it's just got to be compared with the branded drug, and if in say 90% of cases it only is 80 milligrams, it's okay--or 125 milligrams that's okay. You might say why these figures? 80% is 4/5 and 125% is 5/4.

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JM: I see, but the difference between them is over 50%.

VN: Depending on calculations, nearly. Yes, the difference is enormous, so the patient might even be on the same consistent generic so may be taking say 90mg of the equivalent brand drug and stable on it.

But now a new problem may be that the pharmacy has now found a generic company that they can pay less on; or the insurance company might mandate a particular one, because they might find they can pay less. And suddenly you move from even taking 80 milligrams to 125 milligrams--same drug.

Furthermore, the generics might be regarded as equivalent once they've got absorbed and once they've distributed into certain tissues or the blood, but the problem is, they get absorbed at a different stage. So suddenly you're taking your antibiotics, you're taking your tetracycline, and you get as sick as anything and you're nauseated and you have side-effects because it's absorbed too quickly or wrongly.

JM: But if you're on an insurance plan that insists that you take the generic drug, you have no choice!

VN: And this has become the problem. Before one would sometimes at least find insurance plans where you had a $10 copay for your generic and you paid $25 for your brand name and people could make choices. And now a lot of these insurance companies who do not allow some options for branded drug and the generic availability is poor. With due respect, I'm not criticizing them (yet in a way I am) yet if they do this this, it deserves in my humble opinion a certain criticism, when the patient says *"Look I had side effects can't I get the brand name?"* they say "*Of course!"* And you come along and you think you're going to pay $25 and they say *"That'll be $700 for the month"* And you ask *"What do you mean $700?"* And the insurance agent might explain: *"Well, if you look at the small print in your insurance contract we can cover our costs and that's what it's costing us"* It's become unfortunately iniquitous and it's something that we cannot do much about.

People think: *"Well are they saving a lot of money these insurance companies"* but I'm not sure. They may be paying far less for generics but if people are having significant problems or they're having side-effects, they're more likely to be hospitalized, and just that one hospitalization can cost 10 or 200 times as much as that medication ever would cost them. And so we have this whole new fashion in terms of generics.

It's strange because I've had patients where literally the branded drug they would have had to pay a thousand dollars for. Now they just happened to be traveling and working in India or in Italy and for the same drug they're paying five euros or whatever --and you say wait a minute there is something wrong with the whole system!

JM: Well yes, it sounds like this has to be addressed at the system level perhaps through legislation.

VN: Yes, it is a systemic problem and I'm not sure how to solve it because I have the same frustrations with my patients. I can spend hours and hours fighting with companies trying to get my patients to get a decent generic—not even brand drug! And this is amazing.

JM: This is interesting: We've covered a range of issues, a range of drugs, a range of conditions, and we're dealing with it both from the point of view of the patient, the point of view of the doctor, and perhaps the point of view of what needs to be done through legislation.

VN: And maybe the pharmaceutical industry as well. But I suppose I could just describe myself as a 'realistic cynic'. Maybe I'm quite wrong, maybe this is not so; but I speak to a lot of other doctors and they will describe to you the same thing, and others wouldn't care.

JM: Well, I know you're very passionate about this. Thank you, Dr. Vernon Neppe, for sharing your knowledge.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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