

Editorial opinion: principles of prescribing practice in psychiatry and neuropsychiatry

Volume 5 Issue 6 - 2016

Optimizing Prescriptions

As doctors and mental health professionals, a major part of our practice is helping patients. We are clinicians and we need to treat our patients in the best possible way. Effectively, as clinicians, we are also automatically researchers in the health sciences because every case is a new challenge and contains some unique elements-every patient is slightly different. In our clinical practice, we are always taking change into account: In effect, the patients are their own controls and, therefore, we are covertly considering clinical empirical data all the time-effectively, their conditions are monitored by their past health compared with their current and future ones. The question comes up about how we can optimize the pharmacological aspect of our patient management.

For many years I have advocated and taught the following relevant principles:

- I. We prescribe for individual patients taking into account all pertinent factors.
- II. We must apply common sense and appreciate the uniqueness of every one of our patients.
- III. There are always subtle ethicospiritualbiopsychosocialfamiliosocioethnicocultural systems.¹ of influence, and each of these components, in turn, impact on each other.
- IV. Multiple factors impact pharmacological choices, responsiveness to medications and safety issues. Prescription is not just pharmacological.
- V. We need to prescribe for the correct duration and this necessitates evaluating all relevant factors, and appropriate follow-up.

The obvious components written on all patient prescriptions include, hopefully the following appropriate, correct details:

- a. The dose for that patient: this is specific to the circumstances at that time;
- b. The duration of the prescription;
- c. The frequency of the drug.

But there are some major principles that facilitate success in our management of the patient's condition after performing the preliminaries such as detailed evaluation of symptoms and signs, accounting for the key features of the patients' conditions and assessing such features as diagnoses, severity and urgency.

Principle #1: one change at a time

We are scientists practicing a difficult art. Making only one change at a time allows us to predict more accurately (though still with limited success) what might have caused the alteration and assess early responses to that single change. We can make this simpler

by applying specific principles. We can postulate more easily that that alteration might be impacting the change, whether side-effects or improvements. But, in individual cases the rate of alteration in prescription and response varies. We need to be flexible, and allow more rapid or slower changes to fit the circumstances. These revisions could involve subtle changes in dose of a single medication with options including not only increases or decreases in dosing, but different preparations (like another alternative).^{2,3}, or modification of the time of dosing. Such changes also include even adding or subtracting nutritional supplements, or foods.

Sometimes, slow tapers are required. For example, it may take say six or nine months to taper a patient who has taken a selective serotonin reuptake inhibitor (SSRI) for many years.⁴ During that time, other medications might be added, but still there should be only one change at a time on a specific day. Of course, for many other antidepressants, tapering off the drug might be much quicker, taking a few weeks not a few months.

Principle #2: recognize and account for often neglected principles

- i. The need is to maximize success though these suggestions do not appear in the actual written prescriptions.
- ii. We must carefully consider the correct times during the day to take each medication: Sometimes, this is learnt by trial and error-for example, some patients find they need to take their venlafaxine at night to help them sleep; others prefer a morning activation by this medication.
- iii. Similarly, we must know whether each medication should be taken with or without meals.
- iv. Additionally, can they be taken with other medications? For example, we're careful to avoid thyroid supplements taken with calcium as that might diminish absorption. Sometimes situations are far more complex as with liver or kidney malfunction and with drug interactions.⁵

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Received: April 04, 2016 | **Published:** April 19, 2016

- v. Sometimes, the correct frequency during the day can be critical. For example, patients with tardive dyskinesia may report how their movements get worse if there is too large an interval between their doses: The initial tendency may be to increase the dose when we might need to administer their medication targeted at five times per day. Applying another example, the difference between adequate seizure control and the patient having withdrawal seizures or not being covered at certain time of day may simply be one of timing the doses properly.
- vi. We consider carefully the class pharmacological profile of the drug: For example, with antidepressants, we evaluate their potential benefits e.g. making the patient less depressed and often less anxious, as well as the risks e.g. suicidality or mobilization of psychosis. We should specifically look at the side-effects such as sexual dysfunction,^{6,7} headaches and insomnia in SSRIs.⁸⁻¹⁰ This may lead to polypharmacy, simply to manage the side-effects and new medications for side-effects, to get other side-effects.¹¹
- vii. We take into account the delays in complete antidepressant action, typically three to four weeks, recognizing that we may commonly see improvements in that first week in concentration or motivation. But at the same time, we pay attention to self-destructive thoughts being mobilized.
- viii. We should examine the expected success rate for treatment. There is a major difference between statistical and research efficacy, compared with our clinical expectations. An FDA approved drug may be better than placebo, but only successful statistically in 50% or 60% of cases based on double blind studies. As an example, in infections, once we've established the correct etiology (such as bacterial sensitivity), we would expect antibiotics to be successful in say 95% or 98% of cases: Anything less than that success rate may not be acceptable.
- ix. Significant clinical response without significant side-effects is what we're looking for, not the double-blind proof of marginal efficacy that may occur when a drug is approved by the Federal Drug Administration (FDA) in the USA based on two statistically significant studies of active drug over placebo.⁴ Many research studies of psychotropic drugs are prescribed for specific populations, but when appropriately dosed and specifically tailored for individuals, the response rate may be very different and should be much higher. Perhaps we clinicians in the trenches should recognize that marginal double-blind results are of very limited clinical pertinence: Could it be that the art of prescription may be as important as the science?

Principle #3: applying our 21st century advantages

- A. This second 21st century decade has brought about major advances. One is that we must consider the pharmacogenomic components of the patient, such as are the patient's genes showing marked inhibition at the P450 2D6 cytochrome enzyme system? This gene expression markedly affects dosing, and also choice of medication and expectations of response.
- B. Similarly, we must take into account the appropriate drug: Despite the denial by authorities where it is convenient to label all generics equivalent to the branded drug, the generic choices do make a difference. The so-called "80/125 rule" based on areas under the curve, illustrates this.^{2,3} For a drug in the USA to be labeled by the FDA as bioequivalent requires about 90% of

the sample drugs tested based on a special curve to fit within a very wide range namely 4/5 through 5/4 (hence 80% to 125% or the 80/125 rule). Whereas this significant variation may not be too pertinent for some drugs like antibiotics, it can be critically important for patients with cardiac arrhythmias and seizures. Effectively, these generic drugs are only equivalent to a limited degree, and different generics,^{2,3} particularly, may vary widely in pharmacokinetics. Therefore, changing the generic may result in profound implications for the patient: This must be done with care. There are also differences in absorption and side-effects of specific generics versus the branded compounds. Saving money with one generic may come at enormous costs as the patient's condition may be severely compromised.

- C. Nutritional supplements are not just benign additions without side-effects. For example, Vitamin B6 interacts with Levodopa/Carbidopa (Sinemet); over the counter medications (such as Calcium carbonate) may interfere with absorption; and foods such as grapefruit, may interact at the 2D6 level, yet this sometimes may be solved by consistent use of the grapefruit, but we should take into account whatever adjustments are needed.
- D. We should account for absorption and some gastric drugs may affect how much drug is delivered.
- E. We must recognize not only pharmacokinetic drug interactions, but also the kind of interaction: For example, the profound enzyme induction long-term by carbamazepine is very different from its initial inhibition in the first days of administration. By contrast, the marked inhibition of the 2D6 cytochrome enzyme system by fluoxetine or paroxetine may effectively produce a situation pharmacogenomically equivalent to very poor metabolizers.
- F. Moreover, pharmacodynamic interactions are critically important: e.g. selective serotonin reuptake inhibitors markedly increase the serotonin neurotransmitter pool but also may down-regulate the serotonin neurotransmitters so that patients do not respond as much, or lose efficacy. Even more so, such alterations may change the responses to other compounds as a consequence. This makes pharmacological awareness important.
- G. There are other gastronomic confounding factors beyond pharmacological prescriptions: diet, nutritional factors, alcohol or other drugs of abuse are all very important.
- H. There are other non-prescription confounding factors: Outside of the formal prescription, factors like diet, nutrition, and alcohol or other drugs of abuse are very important. For example, we must further recognize that environmental circumstances such as stress, sleep, or travel across time zones, may impact prescription needs. We must also take into consideration the persistent, already present symptoms such as sleep disruption. These symptoms also include features that are drug-induced or pertain to the diagnosis or other conditions. Also, factors such as weight, medical conditions and exercise play roles.
- I. A subtle difference is individual susceptibility: I recognize that possibly 80% of my patients reflect "human" toleration of doses of psychotropic drug. About 10% are "squirrels" who are knocked out with major side-effects when the usual doses in the books are prescribed-these patients sometimes need about a quarter of the usual doses; and about 10% are "elephants" who do not appear even touched by usual doses. These patients need

about triple as much as usual, or even higher doses. However, elephants and squirrels appear, I think, far less common in a general psychological or psychiatric population than in the population I see.

- J. Our clinical experience and knowledge, and careful awareness of the implications of behaviors and the unconscious dilemmas that our patients exhibit, allow us to practice Medicine, Psychology, Consciousness elements, Neuropsychiatry and Psychiatry, as an art as much as a science. If we do not apply that art, and that art is not consonant with our science, we may be short-changing some of our patients. This is not easy because sometimes we are conflicted when the art contradicts the science. Then we must decide what aspects are still in agreement and possibly begin from there. That is a challenge.

Principle #4: Attaining greater therapeutic success

In the choice of medication and dosage, several features help:

- Previous medication responses and non-responses are key and it's worth evaluating details about the previous treatments.
- Family history is often worthwhile and might assist deciding choice of medication.
- Pharmacogenomics is a game-changer. We can genetically test selected patients to establish why they are not responding, what interactions occur in the liver, and what drugs do in the brain at the neurotransmitter level. Although measuring the pertinent genes in the brain and liver is immensely valuable and a great positive in patients with limited medication responsiveness, this advance in testing is not warranted for everyone, because of the costs.
- Delayed effects are important and yet neglected. We expect drugs such as the antidepressants and the antipsychotics to take several weeks to achieve full efficacy. And yet some compounds such as the benzodiazepines like lorazepam, alprazolam, clonazepam or diazepam when used for anxiety, are effectively "quick fix drugs" with later problems: "benefit now, pay later drugs".
- Build up of dosage is pertinent: we may not easily be able to differentiate whether an action relates to time for efficacy, or to the building of dose or combinations. An example here is the gradual build up of Buspirone over several weeks when used out of labeling in tardive dyskinesia.

Principle #5: a prescription is not just a one-time event; it requires appropriate follow-up and awareness of change.

The "mid-course correction" is a key way to evaluate patients over time. This ensures that the treatment can approach optimization.

Monitoring the patient regularly, and requesting frequent feedback is very useful for making minor corrections like dosing or giving advice, including ensuring the patient was following the correct procedures. Such advice and interaction may involve family and close contacts, as well as the patient. One technique is to arrange follow-up a few days later for many prescriptions, or even on the same day or within hours in acute situations.

Do not renew beyond time periods that you're comfortable with. If you do, you run significant clinical and forensic risks for adverse events to occur. Generally, in psychiatry, it is hard to justify renewing psychotropic medications even for the most stable patient, beyond six

months: I will commonly get outpatients back after one or two weeks when prescribing something new or when careful regulation of dose is required.

We must review responses over time to our prescriptions: A common tendency is to regard complaints by the patient as psychologically based, and not as genuine side-effects of the medication. It could be psychological, and it might be that placebo would have produced the same problem unrelated to the medication, but we must assess this carefully over time. Even if there were cogent psychological factors, adjustments are still needed irrespective of the cause if the patient is still complaining about their perceived side-effects.

I've learned over the past four decades, however, not to regard a side-effect as psychological simply because it is rare and unexpected unless all other physical aspects have been taken into account. There must be more data than this: What happens when the patient goes off it? Is it worsened by higher doses? Has the patient retried the drug after going off it? What other factors, including other medication changes, have altered?

In my experience, the purported side-effects are most often actually due to the medications. Most commonly, we need to just drop the dose down if there is a history of previous response, and if not, the major may be better when the drug is discontinued or substituted for another suitable alternative.

Principle #6: the compassionate approach

This editorial would not be complete without a most important point: The compassionate approach. We can do exactly the same with our patient, proving something pharmacologically works, but with results that will vary possibly in proportion to the empathic interest we show our patient. This does not mean spending five times more time with the patient. That may be valuable or destructive or create inappropriate dependency.

The compassionate approach means delivering high quality of care-and that word "care" means exactly that: We try our best. We recognize strengths and weaknesses; and the patient and their family realize we are trying to assist but balancing the complexities of approaches and avoidance that are part of our real world.

We can demonstrate efficacy of an intervention, but such "proof" is better when properly delivered: The patient need not seek the advice of the ones who are callous, even if their advice is exactly the same as clinicians whose advice is delivered with compassion. Intuitive and empathic awareness is frequently the most productive way to deliver news that is not always the best. A percentage of recovery or tolerance of medication or acceptance of a condition is likely to have a better outcome when a patient-centered approach is made a priority.

We must know our patients. Everyone is different. We can give a week's supply of medication to one who is suicidal, but not four weeks. We can trust another patient to comply with the prescription, and build up the dosage carefully: Others may not be able to do that and require extra appointments.

Either way written instructions on new medications (including always requesting the pharmacy to supply the package insert) and details about medication build ups are needed. The patient also recognizes all this as caring for them. And that, for most, is a benefit.

Principle #7: We must merge our research knowledge with our clinical experience

Clinicians recognize that some management will always be out-of-labeling because there simply are no approved drugs for some conditions. This may never change in some instances: Proper trials may cost hundreds of thousands of dollars or more, and it may even be unethical to perform double blind studies because ostensible efficacy and safety in general has already been established. We are not going to see a trial of Aspirin today. Yet, we can never talk about safety in everyone on a particular medication because there may be rare reactions requiring sample sizes of tens of thousands to locate the idiosyncratic, very rare responses. For example, the ostensibly rare lamotrigine major allergic reactions require studying tens of thousands of patients to describe the unusual risks. Realistically, we must be careful, but not distress the patient unnecessarily. That balance can be individualized because not all rules fit all patients.

Principle #8 : We must be particularly vigilant in our ethics relating to using out of labeling medication

Like all management in general in medicine, all prescriptions (outside labeling and also approved medications) should be carefully monitored. It is often valuable recording the balance of the strengths and risks of all our prescribing.

Out of labeling treatment is not disallowed, but should generally be supported on the literature and have the patient's informed consent use of medications outside of FDA approved labeling should involve informed consent. Each case is different but before treatment begins, I regard oral (not written) consent as usually adequate, but there should preferably be a recording in the chart that the prescription being not approved was discussed.

Out of labeling is often the rule in some specialties. Indeed, most drugs prescribed in pediatrics are not FDA approved: There are relatively few studies in children proving safety and efficacy and we take into account experience in other situations. The same applies in pregnancy.

An obvious caution is if there are no medications approved by the FDA (Federal Drug Administration). However, to perform such studies, the pharmaceutical company may deem the costs too high for profitability, or the risk too high.

Ironically, the two examples below relate to areas I pioneered:

I will give two examples of off-label usage that I helped develop. The first is for the condition called "tardive dyskinesia". There are no approved medications and in this instance, there is never likely to be such an approved drug because it would require massive costs to perform a double blind study, and it is unnecessary because there is an ostensibly safe treatment (e.g. high-dose buspirone) which is strongly worthy of consideration, and which has been around for a quarter of a century.^{4,12,13}

A second USA example, from the 1980s is carbamazepine.⁴ It (Tegretol, and later Carbatrol and Eptol) has been approved as an anti-epileptic drug for decades and is efficacious in its indications for epilepsy. It has also been used for the more rare condition of for trigeminal neuralgia. I was fortunate to pioneer the use of anticonvulsants in psychiatry in the early 1980s by using this very drug.¹⁴⁻¹⁹ and, there is little doubt, in my opinion, that Tegretol, the then branded drug, could potentially have been approved for indications like bipolar disorder and dyscontrol anger episodes.

Today, carbamazepine is used off-label as a second-line treatment for bipolar disorder, and in combination with an antipsychotic in some cases of schizophrenia when treatment with a conventional

antipsychotic alone has failed. It also is very useful in aggression dyscontrol.¹⁴ and provisionally, anticonvulsants like lamotrigine are key options in new conditions like paroxysmal behavioral disorder.²⁰⁻²⁹

Yet, why did Tegretol never achieve a formal FDA indication for any condition in psychiatric disorders?

The reason I argue is that carbamazepine had a sinister potential and very rare side-effect relating to serious bone-marrow suppression. I speculate that this may have been the reason for avoiding FDA labeling studies in psychiatry, because it just might have affected its application in seizures if something wrong was found and carbamazepine was just too important in neurology to risk that. Yet, though off label in some psychiatric conditions, clinical experience supports its effectiveness.

Perspective

Prescriptions, including in psychiatry and neuropsychiatry are both an art and a science. We should take account for as much as we can to optimize proper results. This is so whether we are prescribing approved medications or justifying the use of out-of-labeling medications. Clinicians will vary on what principles they prioritize. I have included some basic areas that I regard as important.

1. Principle #1: One change at a time.
2. Principle #2: Recognize and account for otherwise often neglected principles.
3. Principle #3: Attaining greater therapeutic success.
4. Principle #4: Applying our 21st century advantages.
5. Principle #5: A prescription is not just a one-time event.
6. Principle #6: We must be compassionate.
7. Principle #7: We must merge our research knowledge with our clinical experience.
8. Principle #8 : We must be particularly vigilant in our ethics relating to using out of labeling medication.

These principles require continuing to apply "mid-course corrections", and common sense: we should not renew beyond set time periods, and we should recognize that side-effects may commonly be genuine physiological effects and for them to be labeled "psychologically induced" requires the correct dynamics. Clearly, we must also profitably merge our ongoing clinical experience and knowledge with our clinical use.

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