Receptor occupancy and drug response: Understanding the relationship

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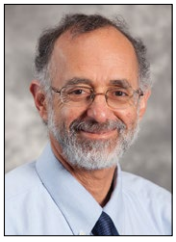

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Most clinicians do not think about receptor occupancy when they prescribe a medication. Most simply assume that if they use a low dose of a medication, they will get a small effect, and if they use a higher dose, they will get a larger effect. However, this is frequently not accurate. Clinicians need to understand the relationship between receptor occupancy and drug response.

In general, when an antagonist of a neurotransmitter receptor is used, it *must* occupy a minimum of 65% to 70% of the target receptor to be effective. This is clearly the case when the target is a postsynaptic receptor, such as the dopamine D2 receptor.[1-3] Similarly, despite significant variability in antidepressant response,[4] blockade of 65% to 80% of presynaptic transport proteins—such as the serotonin reuptake pumps when considering serotoninergic antidepressants,[5,6] or the norepinephrine reuptake pumps when considering noradrenergic agents such as nortriptyline[7]—is necessary for these medications to be effective.

It is reasonable to think of the drug response of such agents as following a "threshold" model (***Figure 1, page 9***). This model makes 2 predictions. The first prediction is that a low dose of the drug might result in <50% receptor occupancy, but is *not* associated with a smaller response; it is simply ineffective. The second prediction is that a very high dose of the drug (eg, one that may exceed 90% receptor occupancy) does *not* result in any additional benefit, but may cause additional adverse consequences.[8]

Alternatively, agonist medications, such as benzodiazepines or opiates, have their efficacy in a continuous dose-dependent fashion (***Figure 2, page 10***). Titrating these medications for clinical response is necessary, and minimal effective doses are highly individual. Agonist medications will not be addressed further in this article.

In this article, the term "response" is used to denote the average (population) symptom change in a study population. This term is not used as clinicians often use it to mean that their specific patient's illness has improved, or that the patient has gone into remission. Furthermore, the information described in this article does not optimize clinical outcome, but instead is intended to help clinicians optimize the use of their pharmacologic tools.

Minimal effective dose

Medications that have a threshold for activity will display that clinically in a *minimal effective dose* (***Table 1,***[3,9] ***page 11*** and ***Table 2,***[5] ***page 12***). The minimal effective dose of medications that act by blocking a neurotransmitter receptor is usually the dose that achieves 65% to 80% receptor occupancy in typical individuals (***Table 2,***[5] ***page 12***). The minimal effective doses for antipsychotics are listed in ***Table 1***[3,9] (***page 11***).

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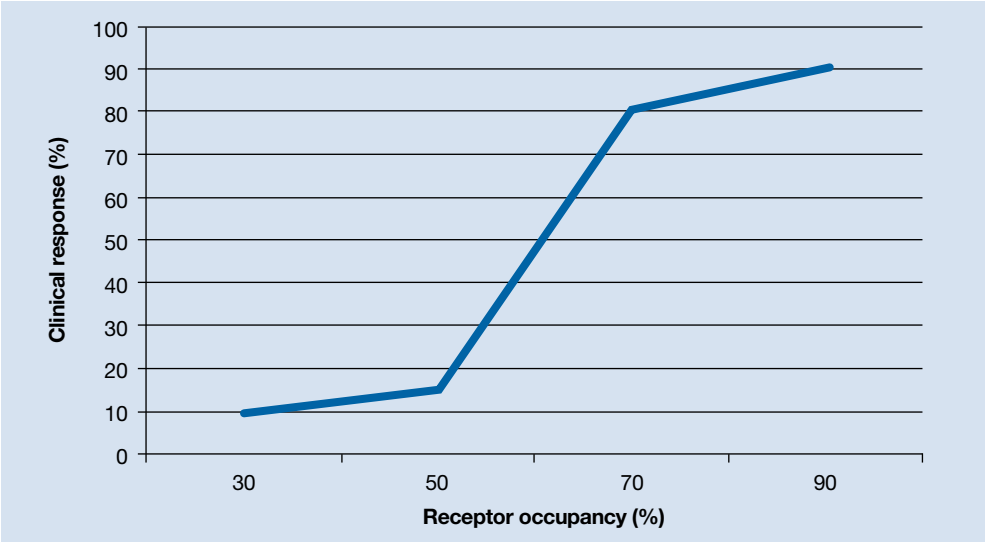
Figure 1

Antagonist agents: The threshold model of receptor occupancy and clinical response



Clinical Point

When an antagonist agent is used, it must occupy 65% to 70% of the target receptor to be effective

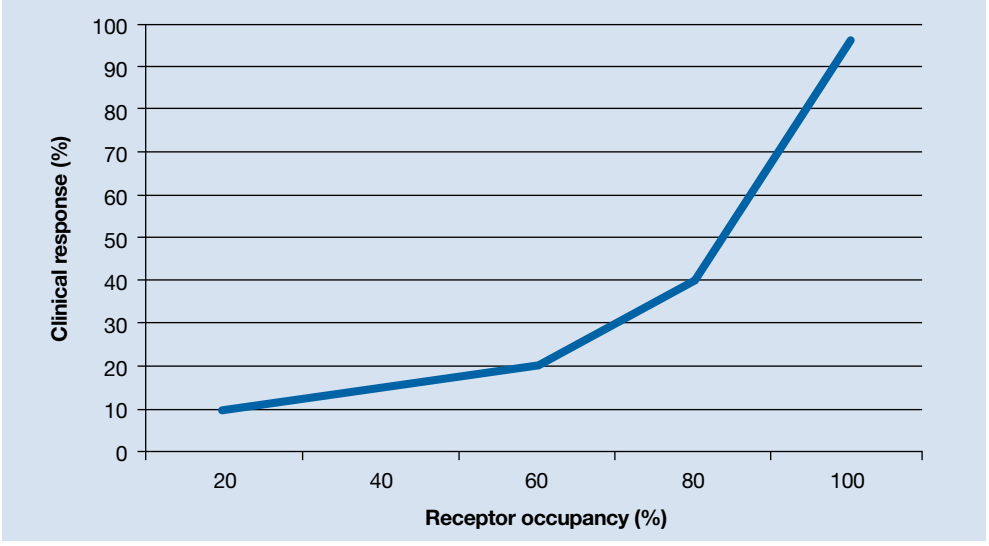
These doses are known to occupy approximately 65% to 70% of postsynaptic D2 receptors in living humans as confirmed by positron emission tomography (PET) scans.[10] Similar minimal effective doses can be determined for serotonin-reuptake inhibiting (SRI) antidepressants (***Table 2,***[5] ***page 12***). In placebo-controlled trials, doses that were smaller than the minimal effective dose did not provide any benefit.

There are important caveats to this. First is the use of partial agonists. Depending on the level of intrinsic activity of a partial agonist and clinical goal, the clinician may aim for a different level of receptor occupancy. For example, aripiprazole will act as a dopamine agonist at lower concentrations, but blocks the receptor at higher concentrations.[11] Unlike antagonist antipsychotics, which require only 65% to 70% D2 receptor occupancy to be effective, aripiprazole receptor binding at effective antipsychotic doses is 90% to 95%.[12-14] Since aripiprazole has an intrinsic activity of approximately 30% (ie, when it binds, it stimulates the D2 receptor to about 30% of the effect of dopamine binding to the receptor[15]), binding to 90% of the receptors, and displacing endogenous dopamine, allows aripiprazole to replace the background or tonic tone of dopamine, which has been measured at 19% in people with schizophrenia and 9% in controls.[16] Clinically, this still appears as the minimal effective dose achieving maximal response[17-19] without significant parkinsonism despite >90% receptor occupancy.[12]

The second caveat is the action of low D2 receptor affinity antipsychotics, such as clozapine and quetiapine. These agents generally achieve adequate D2 receptor occupancy for only a brief period of time.[20] It has been suggested that continuous receptor occupancy at ≥65% may not be necessary to obtain antipsychotic control.[21,22] There may also be specific limbic and cortical (vs striatal) D2 receptor selectivity by clozapine[23] compared with other second-generation antipsychotics such as risperidone and olanzapine,[24,25] although this point remains debatable.[26] Furthermore, the antipsychotic efficacy of low D2 receptor affinity drugs is unreliable, even in controlled, blinded studies (eg, a failed large quetiapine study[27]). Thus far, the actual antipsychotic

Figure 2

Agonist agents: As receptor occupancy increases, so do clinical effects



Clinical Point

For antagonist agents, the minimal effective dose will result in maximal response

mechanism of these agents is yet to be fully understood.

Minimal effective dose achieves maximal response

An interesting aspect of the threshold phenomenon of drug response is that *once the minimal effective dose is reached, maximal response is achieved.* In other words, there is no additional efficacy with additional dose increases. This is readily demonstrated in some studies in which patients were randomly assigned to different fixed doses or dose ranges. In these studies, there was generally no difference in response rates of different doses, so that once 65% to 80% receptor occupancy is achieved, minimal and maximal clinical response is simultaneously reached.[18,28,29]

For example, in the original risperidone studies, 6 mg/d was essentially equivalent to 16 mg/d.[28] Similarly, lurasidone, 40 mg/d, achieves approximately 65% D2 occupancy.[30] When the daily dose is increased to 120 mg, there is no additional benefit in controlling psychosis in schizophrenia.[29] This pattern is also seen in partial agonists, where there are no differences between lower and higher doses in terms of response.[18]

Upon reading this, many clinicians may think "I don't care what the studies say, I have seen additional benefits with additional doses." There are several explanations for this. One is that individual patients have genetic variants that may prevent them from responding in a typical fashion. Hints of this are seen in an apparent disconnect between dosage and drug levels, so that it is not surprising that drug levels are a much better predictor of receptor occupancy than dosage.[31] Nonetheless, as previously pointed out, for a population, dosage does predict receptor occupancy and outcome. However, for individuals, genetic variations make dosages less reliable. For example, ultrarapid metabolizers of cytochrome P450 (CYP) 2D6 may discontinue risperidone due to nonresponse, or require a higher dose or longer time period to respond.[32,33] Similarly, patients who smoke may require an increase in doses of CYP1A2 substrates such as clozapine and olanzapine.[34]

Alternatively, the clinician may note improvement in mood, sleep, appetite, or

other symptoms at lower doses, and then note additional improvements in psychosis or mania at higher doses.[3] This occurs due to the varying affinity of different receptors. For example, in bipolar depression trials that used quetiapine in a fixed-dose design, patients who received 300 or 600 mg/d responded in the same fashion, with no additional benefit in improving depression with the higher dose.[35] Similarly, in a flexible dose range study that evaluated lurasidone in bipolar depression, an average dose of 34 mg/d (range 20 to 60 mg/d) and an average dose of 83 mg/d (range 80 to 120 mg/d) both resulted in the same response (a 15.4-point reduction in depression ratings and an effect size of 0.51).[36] For both quetiapine and lurasidone, higher doses are generally required to control psychosis.[29,37] Note that for lurasidone,

Table 1

Minimal effective dose of second-generation antipsychotics

Agent	Minimal effective dose
Clozapine	400 mg/d
Risperidone	4 mg/d
Olanzapine	15 mg/d
Quetiapine	500 mg/d
Ziprasidone	120 mg/d
Lurasidone	40 mg/d
Aripiprazole	10 mg/d
Iloperidone	6 mg/d
Asenapine	10 mg/d
Haloperidol	8 mg/d

Source: References 3,9

Clinical Point

Patient may have genetic variants that prevent them from responding in a typical fashion

Table 2

Minimal effective dose of serotonin-reuptake inhibiting antidepressants

Agent	Clinically effective dose	Average 5HTTR binding at clinically effective dose	Theoretical minimal effective dose	Estimated 5HTTR binding at theoretical effective dose	Dose that achieves 50% binding at 5HTTR
Fluoxetine	20 mg/d	78.9%	10 mg/d	70%	2.7 mg/d
Sertraline	50 to 100 mg/d	87.8%	25 mg/d	70%	9.1 mg/d
Paroxetine	20 mg/d	79.3%	10 mg/d	65%	5 mg/d
Citalopram	20 to 40 mg/d	78.9%	10 mg/d	70%	3.4 mg/d
Venlafaxine	75 mg/d	85.6%	37.5 mg/d	70%	5.8 mg/d

A minimal effective dose of a serotonin-reuptake inhibiting antidepressant generally requires 65% to 80% receptor occupancy. Doses that achieve 50% receptor occupancy are not partially effective, but are totally ineffective.

Source: Reference 5

Clinical Point

Be willing to reduce a dosage if no additional benefit is seen from higher dosages

agitation, but not psychosis, improves with higher doses, which suggests that recruitment of additional receptors results in improvement in a different set of symptoms.[9]

Clinical implications

The implications for clinicians are relatively clear. Knowing the minimal effective doses for depression, psychosis, or mania informs the target dose. If improvement is seen at lower doses, the clinician needs to assess the profile of symptoms that improved, potential drug–drug interactions, or potential irregularities in the patient's metabolic pathways. Clinicians need to increase doses above the minimally effective dose carefully, and expend additional effort in analyzing changes in their patient's symptoms and adverse effects; this analysis should be performed with skepticism and willingness to reduce a dosage if no additional benefit is seen. Attention to these receptor-symptom interactions will improve response and reduce adverse consequences in the majority of patients.

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Related Resource

- Lako IM, van den Heuvel ER, Knegtering H, et al. Estimating dopamine D2 receptor occupancy for doses of 8 antipsychotics: a meta-analysis. J Clin Psychopharmacol. 2013;33(5):675-681.

Drug Brand Names

Aripiprazole • Abilify	Nortriptyline • Pamelor
Asenapine • Saphris	Olanzapine • Zyprexa
Citalopram • Celexa	Paroxetine • Paxil
Clozapine • Clozaril	Quetiapine • Seroquel
Fluoxetine • Prozac	Risperidone • Risperdal
Haloperidol • Haldol	Sertraline • Zoloft
Iloperidone • Fanapt	Venlafaxine • Effexor
Lurasidone • Latuda	Ziprasidone • Geodon

Clinical Point

Attention to receptor-symptom interactions will improve response and reduce adverse effects