How you can simplify your patient's medication regimen to enhance adherence

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Ms. S, age 53, has bipolar disorder, dyslipidemia, and drug-induced tremor and presents to the clinic complaining of increasing depressive symptoms despite a history of response to her current medication regimen (***Table 1***). When informed that her lithium and divalproex levels are subtherapeutic, Ms. S admits that she doesn't always take her medication. She understands her psychiatric and medical conditions and rationale for her current medications; however, she recently changed jobs, which has affected her ability to adhere to her regimen. Ms. S says the only thing preventing her from adhering to her medication is the frequency of administration.

Only approximately one-half of patients with chronic illness adhere to their medication regimen.[1] Nonadherence has been reported in 20% to 72% of patients with schizophrenia, 20% to 50% of those with bipolar disorder, and 28% to 52% with major depressive disorder.[2] Medication nonadherence can impact a patient's health outcomes[1] and could lead to increased hospitalizations, homelessness, substance use, decreased quality of life, and suicide; however, it is difficult to fully determine the extent of medication nonadherence due to lack of standard measurement methodology.[2]

Factors that affect medication adherence in patients with psychiatric diagnoses include:

- patient-related (ie, demographic factors)
- psychological (eg, lack of insight into illness, negative emotions toward medications)
- social and environmental (eg, therapeutic alliance with the physician, housing stability and support, and discharge planning)
- medication-related (eg, complex dosing schedule).[2]

Medication regimen tolerability, complexity, and cost; patient understanding of medication indications and onset of therapeutic effect; and patient's view of benefits can impact adherence.[1,3] Assessing medication adherence and identifying barriers specific to the patient is essential when developing a treatment plan. If complexity is a barrier, simplify the medication regimen.

Claxton et al[4] found an inverse relationship between medication dosing and

Practice Points

- Assess your patient's adherence to a medication regimen and **discuss barriers to adherence and strategies to resolve them**.
- When developing a treatment plan, **consider ease of administration, dosing requirements, and frequency** to create a simplified medication regimen.
- **Collaborate with a pharmacist and the patient's other prescribers** to assist in simplifying the medication regimen.

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The author reports no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

Table 1

Switching Ms. S's medication regimen

Presenting medication regimen	New regimen
Lithium immediate-release, 300 mg, 3 times daily	Lithium extended-release, two 450-mg tablets at bedtime
Divalproex delayed-release: 250 mg in the morning Two 250-mg tablets in the afternoon Two 250-mg tablets at bedtime	Divalproex extended-release, three 500-mg tablets at bedtime
Propranolol immediate-release, 20 mg, 3 times daily	Propranolol extended-release, 60 mg at bedtime
Trazodone immediate-release, 100 mg at bedtime	Trazodone discontinued
Atorvastatin, 40 mg at bedtime	Atorvastatin, 40 mg at bedtime

adherence. Reviewing data from 76 studies that used electronic monitoring (records the time and date of actual dosing events) the overall rate of medication adherence was 71% ± 17%. Adherence rates were significantly higher with once daily (79% ± 14%) vs 3 times daily (65% ± 16%) or 4 times daily (51% ± 20%), and twice daily (69% ± 15%) was significantly better than 4 times daily dosing. Adherence between once daily and twice daily or twice daily and 3 times daily did not result in a significant difference. The authors noted that electronic monitoring has limitations; patients could have opened the medication bottle but not ingested the drug.[4]

Consider these factors and strategies when developing a treatment plan (***Table 2, page 20***).[3,5,6]

Ease of administration

Medication packaging. Patients with limited dexterity might not be able to remove the medication from blister packaging or child-proof cap, measure non-unit dose liquid preparations, or split tablets in half.[3] Patients with limited patience could get frustrated and skip medications that take longer to remove from packaging or have to be measured. Consult a pharmacist about medication packaging options or formulations that might be appropriate for some patients (ie, individuals with dysphagia), such as oral-disintegrating or sublingual tablets.

Assess pill burden. Although it might not be appropriate when titrating medications, consider adjusting the maintenance dosage to reduce the number of tablets (eg, a patient prescribed divalproex delayed-release, 2,750 mg/d, will take eleven 250-mg tablets vs taking divalproex delayed-release, 2,500 mg/d, which is five 500-mg tablets).

Keep in mind availability of combination medications (eg, olanzapine/fluoxetine) to reduce pill burden. Also, if possible, consider comorbid disease states that allow for prescribing 1 medication that can treat 2 conditions to reduce pill burden (eg, duloxetine for depression and diabetic neuropathy).[3]

Food recommendations. Review food requirements (ie, administration on an empty stomach vs the need for a specific caloric amount) and whether these are recommendations to improve tolerability or required to ensure adequate absorption. Nonadherence with dietary recommendations that can affect absorption may result in reduced effectiveness despite taking the medication.

Administration instructions

Keep administration instructions simple and be consistent with instructions and

Clinical Point

Assessing medication adherence and identifying patient-specific barriers is essential to developing a treatment plan

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Table 2

Administration factors that may affect medication adherence

Factors	Considerations
Medication packaging/ non-premeasured dosage formulations	Removing medication from packaging (ie, blister packaging or child-resistant bottle caps) or use of non-premeasured doses (ie, liquid preparations or tablet splitting) could be difficult for patients with limited dexterity or who are impatient[3]
Pill burden	Be cognizant of available dosage strengths and if the dosage can be adjusted to reduce pill burden Although smaller tablet dosages might be required with initial titration, when a maintenance dosage is achieved, write a new prescription so a higher tablet strength can be dispensed to reduce pill burden Consider combination products (eg, olanzapine/fluoxetine)[3] Consider comorbid disease states that allow for prescribing 1 medication for 2 indications[3] (eg, duloxetine for depression and diabetic neuropathy[5])
Administration requirements	Some medication requirements regarding food can impact tolerability and/or absorption (eg, ziprasidone and lurasidone need to be administered with a specific caloric amount of food to ensure adequate absorption[5])
Instructions	Be aware of patients' literacy and ensure the patient can read and understand instructions before leaving the office Be consistent and specific with instructions
Frequency	Consider formulations that allow for less frequent dosing. Be mindful that some of these formulations may be preferred for tolerability advantages vs extending the dosing interval Divided dosing for some medications may be preferred or required during initial titration; however, during maintenance therapy, you might be able to consolidate the dosage to once daily (eg, risperidone[5]) Review drug information databases or prescribing information to determine an appropriate conversion before switching patients from immediate-release to a longer-acting formulation or to determine if consolidation of maintenance dose is possible Every other day administration might be more difficult to adhere to than once daily Review literature to determine if there is evidence to support less frequent administration (eg, lithium's package insert recommends divided dosing; however, an article by Malhi and Tanious,[6] describes literature evaluating lithium administration once daily and subsequent advantages. The article also enumerates that lithium clearance is lower overnight, so switching from divided doses to once daily administration at bedtime can result in an increase in lithium level up to 25%)

Clinical Point

Consider adjusting the maintenance dosage or using combination medications to reduce the number of tablets

terminology.[3] For example, if all medications are to be administered once daily in the morning, provide specific instructions (ie, "every morning") because it may be confusing for patients if some medications are written for "once daily" and others for "every morning." Some patients might prefer to have the medication indication noted in the administration instructions. Additionally, be aware of the patient's literacy, and ensure the patient is able to read and understand instructions before leaving the office.

Administration frequency

Consider the required administration frequency and the patient's self-reported ability to adhere to that frequency before initiating a new medication. Ask the patient what frequencies he (she) can best manage and evaluate his (her) regimen to determine if a less frequent schedule is pos-

sible. Consider formulations that may allow for less frequent dosing (eg, controlled-release, sustained-release, long-acting, or extended-release formulations) or consolidating divided doses to once daily if possible.[3] Some of these formulations may be preferred for tolerability advantages vs extending the dosing interval (eg, regular-release and extended-release lithium tablets have the same half-life of approximately 18 to 36 hours; however, the extended-release formulation has a longer time to peak serum concentration, approximately 2 to 6 hours vs 0.5 to 3 hours, respectively. As a result, the extended-release formulation may offer improved tolerability in terms of peak-related side effects,[5,7] which may be advantageous, especially when dosing lithium once daily). Keep in mind, for some patients every other day administration is more difficult to adhere to than once daily.

Review drug or prescribing information to determine an appropriate conversion before switching from an immediate-release to a longer-acting formulation. The switch may result in different drug serum concentrations (eg, propranolol sustained-release has different pharmacokinetics and produces lower blood levels than the immediate-release formulation). When switching between formulations, monitor patients to ensure the desired therapeutic effect is maintained.[8]

Consider collaborating with pharmacists, primary care providers, and other prescribers to simplify medical and psychiatric medications.

Other considerations

Lab monitoring requirements for drugs, such as clozapine, lithium, or divalproex, could affect a patient's willingness to adhere. Use of weekly or monthly medication organizers, mobile apps, alarms (on cell phones or clocks), medication check-off sheets or calendars, and family or friend support could help improve medication adherence.

Related Resource

- Gottlieb H. Medication nonadherence: finding solutions to a costly medical problem. www.medscape.com/viewarticle/409940.

Drug Brand Names

Atorvastatin • Lipitor
Clozapine • Clozaril
Divalproex • Depakote
Duloxetine • Cymbalta
Lithium • Eskalith, Lithobid
Lurasidone • Latuda
Olanzapine/fluoxetine • Symbax
Propranolol • Inderal
Risperidone • Risperdal
Trazodone • Desyrel
Ziprasidone • Geodon

CASE CONTINUED

After reviewing the medication regimen and consulting with a pharmacist, Ms. S's regimen is simplified to once-daily administration, and pill burden is reduced by using extended-release formulations and consolidating doses at bedtime (***Table 1, page 19***). Additionally, trazodone is discontinued because divalproex, now taken once daily at bedtime, is sedating and aids in sleep.

For medications that require therapeutic blood monitoring such as lithium and divalproex, check drug levels when switching formulations. In the case of Ms. S, lithium, propranolol, and divalproex dosages were switched to extended-release preparations and consolidated to once daily at bedtime; the divalproex dosage was increased because an increase in total daily dose between 8% to 20% may be required to maintain similar serum concentrations.[5] Lithium immediate-release was switched to the extended-release, which reduced the pill burden and could help tolerability if Ms. S experiences peak concentration-related side effects. Consolidating the lithium dosage from divided to once daily at bedtime can increase the lithium serum level by up to 25%.[6]

With a change in formulation, monitor tolerability and effectiveness of the medication regimen in regard to mood stabilization and tremor control, as well as check serum lithium and divalproex levels, creatinine, and sodium after 5 days, unless signs and symptoms of toxicity occur.

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Clinical Point

Keep administration instructions simple and be consistent with terminology

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