The art and science of drug titration

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Abstract

A "one-size-fits-all" approach has been the standard for drug dosing, in particular for agents with a wide therapeutic index. The scientific principles of drug titration, most commonly used for medications with a narrow therapeutic index, are to give the patient adequate and effective treatment, at the lowest dose possible, with the aim of minimizing unnecessary medication use and side effects. The art of drug titration involves the interplay of scientific drug titration principles with the clinical expertise of the healthcare provider, and an individualized, patient-centered partnership between the provider and the patient to review the delicate balance of perceived benefits and risks from both perspectives. Drug titration may occur as up-, down-, or cross-titration depending on whether the goal is to reach or maintain a therapeutic outcome, decrease the risk of adverse effects, or prevent withdrawal/discontinuation syndromes or recurrence of disease. Drug titration introduces additional complexities surrounding the conduct of clinical trials and real-world studies, confounding our understanding of the true effect of medications. In clinical practice, wide variations in titration schedules may exist due to a lack of evidence and consensus on titration approaches that achieve an optimal benefit-harm profile. Further, drug titration may be challenging for patients to follow, resulting in suboptimal adherence and may require increased healthcare-related visits and coordination of care amongst providers. Despite the challenges associated with drug titration, it is a personalized approach to drug dosing that blends science with art, and with supportive real-world outcomes-based evidence, can be effective for optimizing pharmacotherapeutic outcomes and improving drug safety.

Plain language summary

The art and science of finding the right dose

Summary: Changes to medication doses to achieve the best clinical response is known as drug titration. Drug titration is a way for clinicians to personalize medication doses so that patients can obtain the intended benefits of the treatment of their disease while minimizing side effects. This can occur by increasing the dose of a medication over time (up-titrating) until symptom relief occurs or a certain laboratory value is met, indicating that the most appropriate dose for that patient has been found. On the other hand, it can mean decreasing the dose of a medication over time (down-titrating) to lessen side effects or to find the lowest possible dose that keeps a patient's symptoms or laboratory values under control. At times, up- and down-titrating may occur at the same time when one medication is being stopped and another is being started (cross-titration). For many medications, there may be limited scientific evidence to guide clinicians on the best schedule for changing medication doses. Further, dose changes can be difficult for clinicians to explain and for patients to follow. In addition, without proper coordination of care between providers, it may be difficult to properly manage adverse effects. Electronic health record systems need to implement new structures that capture medication dose changes, allowing better coordination of care and titration studies to identify schedules that achieve better patient outcomes and improve medication safety.

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Introduction

Establishing the precise dose for a drug is a complex process. Historically, a single-dose regimen has been selected for agents with a wide therapeutic window, as minor changes in drug concentrations would have a limited impact on the efficacy and safety of the medication.[1–3] However, a single-dose "one-size-fits-all" approach may not be equally effective and safe in all patients, and, therefore, multiple patient-level factors likely influence the optimal dose for an individual patient. Individual patient characteristics, including genetics, age, weight, renal and hepatic function, co-morbidities, and co-administration of other drugs, affect the dose a particular patient may require for a favorable risk–benefit ratio.[4,5] In addition, pharmacokinetic (PK) (dose-concentration relationship) and pharmacodynamic (PD) (concentration-effect relationship) factors affect the amount of drug required,[2,4,6] including absorption, bioavailability, distribution, metabolism, and excretion, along with the mechanism of action and the magnitude and duration of the clinical effect of the drug.[5,7]

Drug titration is a more individualized, patient-centered approach to dosing, and is used in multiple therapeutic areas. Drug titration is common for agents with a narrow therapeutic index in order to optimize the therapeutic benefit while minimizing the risk of adverse effects, including drug–drug interactions.[3,5] Some classic examples of drugs that require titration include antibiotics (e.g., aminoglycosides, vancomycin),[8,9] anticoagulants (e.g., warfarin),[10] anticonvulsants (e.g., phenytoin),[11] antidepressants (e.g., paroxetine),[12] antidiabetics (e.g., insulin, metformin),[13] antipsychotics (e.g., quetiapine),[14] opioids (e.g,. morphine),[15] and stimulants (e.g., amphetamines).[16] In this narrative review, we discuss types of drug titration, titration schedules, challenges in drug titration, and opportunities to improve the art and science of drug titration.

Drug titration

Drug titration versus dose adjustment

Drug titration may be based on PK/PD parameters, achievement of therapeutic outcomes, results of pharmacogenetic testing (PGT), and/or maintenance of drug safety.[2,3,17] It is important to keep in mind the distinction between drug titration and dose adjustment. A dose adjustment is necessary to maintain appropriate drug concentrations despite alterations in PK/PD parameters due to innate or external factors such as age, body weight (actual, ideal, or adjusted), drug interactions, metabolism, plasma protein binding, or renal/hepatic impairment.[2,3] Dose adjustment recommendations can be found in prescribing information and usually occur without a titration. For example, the dose of intravenous ciprofloxacin for an adult patient with chronic renal failure on hemodialysis is 400 mg every 24 h as compared with a dose of 400 mg every 12 h when a patient's creatinine clearance (Cl_{cr}) is >30 ml/min for most infections.[18,19] The recommended dose of rimantadine for influenza A prophylaxis in the elderly is 100 mg orally daily (as opposed to twice daily), and the high-dose influenza vaccine is specifically approved for patients 65 years and older.[20,21] The administration of efavirenz and voriconazole concurrently is an example of a dose adjustment based on a drug–drug interaction. Efavirenz [always administered in combination with other antiretrovirals to provide a complete human immunodeficiency virus (HIV) regimen] is adjusted down to 300 mg/day orally when it is administered simultaneously with voriconazole, and the voriconazole dose is increased to 400 mg orally every 12 h.[22] Lastly, ethambutol illustrates a dose adjustment based on weight: for patients weighing 40–55 kg, the recommended daily oral dose is 800 mg, for patients weighing 56–75 kg, the dose is 1200 mg, and for patients weighing 76–90 kg, the dose is 1600 mg.[23]

Drug titration, in the traditional, scientific sense, is a change in dosing based on a specific PK/PD, clinical, pharmacogenetic, or laboratory parameter, or is based on a set titration schedule as per the prescribing information. It is dosing that is individualized to the specific patient, with the goal of reaching a specific laboratory or clinical target with the lowest dose possible, while mitigating adverse effects, and/or preventing withdrawal/discontinuation symptoms or disease recurrence. It may be accomplished *via* up-titration (increasing

the dose over time), down-titration (decreasing the dose over time), or cross-titration (decreasing the dose of one drug while at the same time increasing the dose of another drug).[3] A classic example of titration is the dosing of aminoglycosides and vancomycin based on therapeutic drug concentrations. In general, gentamicin is dosed based on ideal body weight, starting with a loading dose of 1.5–2 mg/kg intravenously, followed by 1–1.7 mg/kg (3–5 mg/kg/day) every 8 h with subsequent dose adjustments based on peak and trough concentrations and the minimum inhibitory concentration (MIC) of the bacterial pathogen.[8] The goal is to maximize the peak concentration to MIC ratio (⩾8:1–10:1) to optimize bacterial killing.[24] Vancomycin is dosed based on actual body weight, starting with a loading dose of 20–35 mg/kg in critically ill patients, followed by 15–20 mg/kg/dose every 8–12 h with subsequent dose adjustments based on the ratio of the area under the curve (AUC) to the MIC of the bacterial pathogen.[9] The aim of this dosing strategy is to sustain an AUC/MIC ratio of 400–600 for methicillin-resistant *Staphylococcus aureus* infections to have the best chance of clinical treatment success with decreased potential for nephrotoxicity.[9] Further, PGT plays a role in tailoring both drug selection and dosing with the intent of optimizing effectiveness and minimizing adverse effects.[17] PGT has been shown to be potentially helpful in these respects with anesthetics, anticonvulsants, antidepressants, antineoplastics, antiretrovirals, attention deficit hyperactivity disorder (ADHD) medications, mood stabilizers, and warfarin.[17,25–31]

The art versus science of drug titration

The scientific principles of drug titration are to give the patient adequate and effective treatment, at the lowest dose possible, with the aim of minimizing unnecessary medication use and side effects.[2,3] The art of drug titration involves the interplay of scientific drug titration principles with the clinical expertise of the healthcare provider, and an individualized, patient-centered partnership between the provider and the patient to review the delicate balance of perceived benefits and risks from both perspectives. The art therefore takes into consideration what is realistic for a particular patient, including the intended therapeutic outcomes and management of drug titration based on each patient's unique circumstances. This is an individualized approach that includes compromise and recognizes the patient's autonomy, and evaluates the impact of positive and negative clinical outcomes, not just PK/PD and laboratory measurements. The patient factors that should be taken into account during the decision-making process may include, but are not limited to, the titration complexity, the patient's expectations related to drug effectiveness and when therapeutic outcomes should occur, the severity of the disease, co-morbidities, concurrent medications, consequences of non-adherence, potential for and seriousness of adverse effects, personal priorities, health literacy, and socioeconomic status. These factors inherently influence a patient's willingness to adhere to a drug titration schedule, without which the benefits of the medication will not come to fruition.[3,32–35] Artistry, rooted in scientific evidence, is used to select the most appropriate titration schedule for an individual patient, in particular when multiple strategies exist or strategies are less well-defined.

Titration schedule

The information regarding how to manage drug titration is usually provided in the prescribing information for the drug, evidence-based clinical practice guidelines, or various drug information resources. For some medications, set titration schedules may be recommended by the manufacturer, as found in the product label. Dose packs facilitate adherence by providers and patients to these recommended titration schedules, as seen with methylprednisolone and azithromycin.[3,35–37] Alternatively, response-guided titration may be used alone or in combination with target titration schedules per the package insert, as with antiepileptic drugs.[38] Ideally, for a response-guided approach to titrated drug dosing, there is an objective marker to measure the laboratory or clinical parameter of interest that guides the titration schedule.[2] Example laboratory markers that guide titration include target international normalized ratio (INR) with warfarin,[39] target phenytoin concentration with phenytoin,[11] and target blood glucose concentrations during daily testing and hemoglobin $A1_c$ for long-term monitoring with insulin and oral diabetes medications.[40] When available, dosing algorithms based on PGT can be used to optimize the dose for individual patients, as has been demonstrated with warfarin and phenytoin.[10,41,42] Clinical parameters may also be used to facilitate drug titration. Examples include antiepileptic drug doses titrated based on the reduction in seizure frequency or seizure

freedom,[43] and antidepressants or opioids titrated based on scales that assess clinical response, such as the Hamilton Depression Rating Scale or the Visual Analog Scale, respectively.[12,15]

Providers may need to make exceptions to recommended titration schedules and treatment goals as they may not meet the needs of all patients. The recommendations may be used as a starting point, with modifications made based on a patient's specific needs. For example, when treating diabetes, hypertension, and hypercholesterolemia, the adverse effect profiles of the drugs used to treat these diseases influence how aggressive or cautious providers and patients may want to be with drug doses and titration schedules. There may be compromises to allow some degree of hyperglycemia to decrease the risk of hypoglycemia, some degree of hypertension to minimize the risk of hypotension, and some degree of hypercholesterolemia to prevent liver enzyme elevations or myopathy.[1] This type of customization, which showcases drug titration as a fusion of science and art, is necessary to achieve effectiveness and maintain patient safety.

Up-titration

Up-titration is characterized by initiating therapy at a lower dose and increasing the dose over time to maintain or attain a specific response, or to decrease the risk of adverse effects. An example of up-titration to a specific therapeutic goal is the use of norepinephrine in the setting of sepsis and septic shock. The dose of norepinephrine is titrated up to achieve a mean arterial pressure of 65 mmHg.[44] Another example is semaglutide for the treatment of type 2 diabetes. The dose of semaglutide is titrated up to achieve glycemic control. Starting with an initial dose of 0.25 mg subcutaneously once weekly for 4 weeks, the dose is then increased to 0.5 mg once weekly for at least 4 weeks, and further increased to 1 mg once weekly if needed.[45] Likewise, the oral semaglutide formulation also requires up-titration, beginning with a dose of 3 mg orally once daily for 30 days, followed by 7 mg orally once daily for 30 days. If additional glycemic control is needed, the dose may be increased to 14 mg orally once daily thereafter.[46] With up-titration towards a specific therapeutic goal, it is important to keep in mind that there may be a point at which there is a ceiling effect in the response and continuing to increase the dose will not increase the effect, and may, in turn, put a patient at higher risk of adverse effects.[3]

Up-titration may be used to mitigate adverse effects. An example in oncology is the recommended titration schedule for venetoclax, an agent used for the treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma. In order to prevent tumor lysis syndrome from occurring, dosing with venetoclax is initiated at 20 mg/day orally in week 1, then increased to 50 mg/day in week 2, 100 mg/day in week 3, 200 mg/day in week 4, and then 400 mg/day in week 5.[47] Antiepileptic drugs are also up-titrated to minimize adverse effects. Perampanel dosing is started at 2 mg/day orally at bedtime with an up-titration of 2 mg per week to achieve a target of 4–12 mg/day to minimize dizziness.[43] Lamotrigine is gradually up-titrated to reduce the risk of rash, in particular Stevens-Johnson syndrome or toxic epidermal necrolysis. There are 5-week starter kits available to assist patients with adherence to the titration schedule and specific dose titrations are recommended based on the patient's age, weight, and concurrent medications.[48] Antidepressants are another class of drugs that require up-titration to reduce adverse effects. Selective serotonin reuptake inhibitors are started at a lower dose and up-titrated over time to reduce the development of anxiety.[49]

Up-titration may also be necessary based on a specific PK/PD parameter. Carbamazepine undergoes self-induction of hepatic enzymes, which leads to an increase in its metabolism over time, thereby requiring an increase in dose over time in order to maintain appropriate concentrations and a therapeutic effect.[50] In contrast, patients with genetic variants of the cytochrome P450 enzymes *CYP2C9*2* and *CYP2C9*3* have a reduced ability to metabolize warfarin. Patients with these variants should be initially treated with a lower dose of warfarin and up-titrated more cautiously as they are at higher risk of developing supra-therapeutic international normalized ratios (INRs) and adverse effects.[10]

Up-titration may also be used for gradual improvement of symptoms or clinical outcomes while monitoring for adverse effects, particularly when optimal clinical effectiveness comes at the cost of dose-related side effects for drugs with

relatively narrow and specific therapeutic windows.[3] The art is in the partnership between the provider and patient for the management of side effects and occurs through the assessment of patient expectations and tolerance, as related to both presence and severity of negative effects. Therefore, the art includes the evaluation of any problems that the patient is experiencing to determine whether the dose is too high, too low, of insufficient duration to experience positive effects and/or for side effects to subside, and/or ineffective for that particular patient. This is demonstrated in the treatment of ADHD, whereby treatment guidelines recommend four different approaches to up-titration: increasing the dose up to a dose beyond which there is no further improvement in symptoms, increasing the dose until the lowest dose that provides a response is achieved, increasing the dose until the maximum dose is reached, or increasing the dose until adverse effects occur.[51] The success of the approach chosen relies on communication between the provider and the patient at the onset of titration, continual input from the patient over the course of the titration, and a mutual understanding of the need for flexibility in the up-titration schedule to maintain patient adherence.[3] Based on the information the patient provides regarding symptom control and tolerability, the provider can alter the titration if doses are sub- or supratherapeutic. For this to occur, it is critical to have the patient's (or patient proxy, e.g., parent) assessment of the level of effectiveness of their functioning on different doses so subsequent titration is guided by input from the patient.

Down-titration

Down-titration is characterized by decreasing the dose over time once a specific response has been achieved, to either maintain a specific response while decreasing the risk of adverse effects or to prevent withdrawal or discontinuation syndromes. There are many examples of medications for immunologic and inflammatory diseases that may require a dose decrease once their specific therapeutic goal has been achieved. Infliximab is a tumor necrosis factor inhibitor used to treat rheumatoid arthritis.[52] In patients with stable low disease activity or disease remission, infliximab may be down-titrated from a dose of 3 mg/kg intravenously over time in order to discontinue the drug, although some patients may experience disease flares during this tapering process.[52]

The dosing of corticosteroids also highlights a down-titration approach. When corticosteroids are used for anti-inflammatory or immunosuppressive effects, for instance, in the treatment of asthma exacerbations, giant cell arteritis, rheumatoid arthritis, or systemic lupus erythematosus, they usually require an initial short course with dosing at the higher end of the dosing range to achieve prompt control of symptoms. This is then followed by gradual dose reductions over time to the lowest dose that maintains the clinical response or eventual discontinuation, thus minimizing the serious side effects that can occur with long-term use of corticosteroids.[36,53–56] A specific example in allergic conditions is the use of a methylprednisolone dose pack that starts with 24 mg orally on day 1, 20 mg on day 2, 16 mg on day 3, 12 mg on day 4, 8 mg on day 5, and ends with 4 mg on day 6.[54,55] In these cases, down titration is utilized when rapid control of a disease process is important and risks of acute toxicity from high doses are minimal, but there is significant risk of harm associated with extended use of higher doses or with use at any dose for long durations.

Down-titration is also a method to prevent withdrawal or discontinuation syndromes and/or other adverse effects. One example of this is the tapering of prednisone in patients receiving >20 mg/day orally (or the equivalent doses of other corticosteroids) for >3 weeks to prevent hypothalamic-pituitary-adrenal axis suppression.[56,57] Another instance is the down-titration of antidepressants by decreasing the dose over several weeks to prevent the discontinuation syndrome that may occur when stopping the medication.[49] Lastly, tapering the doses of benzodiazepines gradually over approximately 4–8 weeks or more also illustrates the down-titration approach to decrease the risk of benzodiazepine withdrawal syndrome, which may include the development of seizures. Down-titration may also be based on a specific PK/PD parameter. As renal function declines over time, such as in the setting of acute kidney injury, certain drugs will be titrated based on the Cl_{cr}. For instance, when famotidine is used for the treatment of gastroesophageal reflux disease, it is given as 20 mg orally twice daily. In the setting of renal impairment,

famotidine is given as 20 mg once daily when the Cl_{cr} is 30–60 ml/min and adjusted down to 20 mg every other day or 10 mg once daily when the Cl_{cr} is <30 ml/min. This approach is used to reduce the risk of adverse effects as the renal function declines.[58] Changes in plasma protein binding of a drug may also necessitate a dose titration. Phenytoin concentrations need to be adjusted in patients with low albumin, which may then lead to the need for a decreased dose of phenytoin in order to lower the risk of supra-therapeutic concentrations and adverse effects.[11]

Down-titration poses a unique challenge as patients may be reluctant to decrease doses or discontinue drugs that have provided symptom control. Further, patients may not want to experience withdrawal or discontinuation syndromes. With down-titration, the provider must be skillful in assuring the patient that the rate of down-titration can be adjusted as needed and additional interventions can be used to help manage symptoms related to decreasing the dose.[59,60] Like up-titration, providers may craft their own down-titration regimens when there is a lack of defined schedules, as with antidepressants, benzodiazepines, biologics, and corticosteroids.[36,52,56,59,60] The down-titration schedule is designed based on symptom severity, the urgency with which symptom relief is needed, the degree of clinical response, prior experience in clinical practice and/or in an individual patient, and the risks associated with recurrence of symptoms.[52,54]

Cross-titration

Cross-titration (or cross-tapering) in either direction may be performed when switching patients from one medication to another or to enable patients to be maintained on two medications, at times allowing both to be used at lower doses than when given alone.[3,59] In the setting of cross-titration, both evidence-based resources and clinical expertise that apply to up- and down-titration need to be considered for each individual drug and patient, plus scrutiny regarding the safety of using two specific drugs concomitantly, with particular consideration given to adverse effects and drug interactions. A case in point is the titration of lamotrigine when a patient is concurrently taking valproate. In this setting, lamotrigine is titrated up, starting at a lower dose (25 mg every other day rather than 25 mg daily) than when prescribed alone. This titration schedule is adjusted to account for the interaction between the two agents that decreases the clearance of lamotrigine.[48] Adding vasopressin, up to 0.03 units/min, to decrease the norepinephrine dosage in sepsis and septic shock is an example of using a lower dose of one agent when it is used in combination with another drug. Using the drugs in combination allows a lower dose of norepinephrine to be used while still maintaining mean arterial pressure. The benefit of this approach remains uncertain as no difference in mortality was found in the clinical trial that evaluated this practice. However, a subgroup analysis suggested improved survival in patients who received vasopressin with norepinephrine doses <15 µg/min.[44] Lastly, cross-titration when switching antidepressants highlights a down-titration of the current agent until it can be discontinued while concurrently starting a new agent and up-titrating its dose over time.[59] This customized approach allows continued control of depression symptoms and avoidance of the antidepressant discontinuation syndrome.[59]

Complexities of drug titration

Evidence

Drug titration is a form of personalized medicine.[2] There is mounting evidence that substantial treatment heterogeneity exists in both clinical trials and real-world practice. This contradicts the notion that all patients being treated with a specific medication actually take the same dose, for the same duration, and in combination with the same concomitant medication(s).[61–63] While it is becoming clearer that a "one-size-fits-all" approach is not optimal for drug dosing,[17] clinical trials with titrated medications are complex, as comparisons between fixed-dose and dose-titration or between various dose-titration schedules, are difficult to study. Such challenges include the maintenance of blinding, external validity, and increased potential for post-randomization biases (i.e., differential loss to follow up, differential adherence, and differential discontinuation).

In addition, it is difficult to establish real-world evidence for titrated medications. When patients do not have the same drug exposures (drug, dose, duration, and concomitant medications), it is difficult to attribute specific clinical outcomes to

specific exposures. This challenge has been described in infectious diseases, in which it was found that treatment heterogeneity is nearly universal in bloodstream infections.[62] Unfortunately, there is a lack of real-world exposure data for titrated medications, as data sources lack titration details. As a result, it is difficult to substantiate titration schedules, in terms of safety or effectiveness, since supportive data are unavailable. Therefore, drug titration complicates our understanding of the effect of medications in real-world practice.

Due to the lack of real-world evidence for titrated medications, clinicians often must rely on data from clinical trials to inform their prescribing of schedules for drug titration, despite the aforementioned clinical trial limitations. However, it is unclear whether titration schedules closely reflect titration from clinical trials and/or labeled titration, and some evidence suggests not only wide variation in titration schedules in clinical practice, but also divergence in titration schedules from clinical trials.[43] For instance, a meta-analysis determined that, out of 11 randomized clinical trials and 38 cohort studies of methylphenidate for the treatment of ADHD in children, only 2 and 8, respectively, reported their justification for the dose range used in the study.[64] However, the justification was either unclear or did not match the cited source in most of these studies, highlighting the lack of evidence supporting titration schedules of methylphenidate in ADHD. In addition, there was a wide variation in the dose titration as the dose in the randomized clinical trials ranged from 20 to 72 mg/day, whereas in the cohort studies, it ranged from 20 to 60 mg/day.[64] Also, in patients on medications for heart failure, it was found that the up-titration schedules carried out in clinical trials by dedicated research staff are not mirrored in the real-world setting, where lower doses are generally prescribed in contrast to the higher doses achieved in clinical trials.[65]

Consensus

There may be a lack of consensus on titration schedules that maximize benefits and minimize harms,[3,49] or a lack of consensus on the therapeutic and toxic concentration of the medication.[3,11] One example of a drug that has indication-based titration schedules is quetiapine. The initial dose and dose increases for the titration are dependent on whether the drug is being used for schizophrenia, bipolar mania, or bipolar depression.[14] Antiepileptic drugs demonstrate variability in therapeutic *versus* toxic drug concentration ranges. Some patients may experience seizure freedom at concentrations that are below the defined reference range, while others may have a reduction in seizures only when the concentrations are above the range, thus suggesting that each patient has his or her own individual target concentration.[11] This highlights that, although there may be a recommended titration schedule stemming from a "one-size-fits-all" approach based on prescribing information or clinical guidelines, providers may need to craft a titration regimen to best fit the needs of an individual patient.

The benefits of up-titration to attain a specific response with certain medications has been uncertain. In 2002, the recommendation for patients undergoing elective noncardiac surgery per the American College of Cardiology/American Heart Association Guideline for Perioperative Cardiovascular Evaluation for Noncardiac Surgery was to prescribe a beta-blocker days or weeks before surgery and titrate the dose to achieve a heart rate of 50–60 beats/min.[66] However, in the 2014 guideline update, the recommendation was modified as the benefit of starting beta-blockers in naïve patients prior to surgery was called into question along with how to titrate them in this setting.[67] Such uncertainly also exists with tapering (down-titrating) antidepressants. While some clinicians suggest decreasing the dose by 25% per week until the antidepressant is discontinued, others recommend decreasing the dose by 25% per month.[59] The protocol for benzodiazepine down-titration is also not well defined, as the recommendations range from decreasing the dose by 50% each week to decreasing it by 10–25% every 2 weeks.[60] Lastly, there may be an inability to measure objective outcomes without a specific marker for efficacy, effectiveness, or toxicity.[2]

Adherence

Further complicating the effectiveness and safety of drug titration is the inconvenience to the patient, which can impact medication adherence, including under-dosing (delay or failure to increase dose), over-dosing (initial high dose or

rapid dose increases), and/or missed dosing. Drug titration is also inconvenient in terms of healthcare-related visits for dose titrations and/or monitoring.[1] Up to half of patients are non-adherent to their chronic medications, without taking into account the additional challenges surrounding dose titration,[3,68] and non-adherence is associated with harmful health consequences and increased healthcare costs.[17,35] As described earlier, patients may not take their medications or may not take them as prescribed, for numerous reasons, which includes complex regimens and adverse effects.[3,35]

Starter kits and dose packs, such as those mentioned previously for lamotrigine and methylprednisolone, help to facilitate adherence to specific drug titration schedules.[3,35,48,54,55] Titration packs are convenient for the provider and the patient, making it easier to adhere to a titrated regimen. However, they may not meet the needs of all patients, and, in some cases, may inadvertently cater to a "one-size-fits-all" approach and interfere with personalized dosing.[54,55]

Although drug regimen complexity is recognized as a risk factor for non-adherence with certain medications, up-titration or down-titration also alleviates adverse effects, as has been described with antidepressants and anticonvulsants, potentially leading to improved adherence by reducing treatment interruptions or discontinuations.[12,38,49,69–71] The need to coordinate care among providers and between providers and patients becomes more critical with drugs that require titration, both to monitor for effectiveness (or lack thereof) and adverse effects and to facilitate dose titration.[3,65] However, clinicians have limited time, inadequate support structures, and unclear roles regarding drug titration.[65]

The complexities of drug titration affecting medication adherence are further complicated by multi-morbidity. Overall, medication utilization rates have increased over time, due to increases in available medications on the market to treat diseases (e.g., medications for certain conditions were not previously available), as well as increased rates of chronic diseases due to the changing health and life expectancy of the population (increase in chronic diseases such as diabetes, high blood pressure, high cholesterol, and greater multi-morbidity in aging populations). Data from the 2010 National Health and Nutrition Examination Survey (NHANES) found that approximately 39% of people who are at least 65 years of age were taking at least five prescription medications.[72] Patients taking complex medication regimens have been shown to have worse medication adherence and patient outcomes. The addition of medications requiring titration adds further complexity to medication regimens for patients, making it more difficult to understand the dose and schedule, and, in turn, can reduce patient adherence.[1,3,35]

Various strategies have been deployed to improve and support drug titration in clinical practice. A multidisciplinary healthcare approach can help improve the quality of medication titration. In the setting of heart failure, clinician education, decision support and communication tools, post-prescribing telephone monitoring of patients, auditing of clinicians, transitions of care and disease management services, and expanded prescribing privileges for nurses and pharmacists have been used to enable a more individualized approach to pharmacotherapy.[65] In addition, nurse-led titration services of heart failure medications have achieved target doses sooner while decreasing heart failure-related hospital admissions and increasing patient survival.[73] Multidisciplinary teams that combine elements of the above-described approaches that take into account the best fit for the specific clinical practice site are more likely to be successful.[65] Several studies have shown that pharmacist run titration services for insulin in patients with diabetes mellitus have resulted in improved glycemic control.[74,75] Similar programs utilizing pharmacists have been effective in the management of anticoagulation, neurologic conditions, and gout.[76–78] Appropriate drug titration that results in better patient outcomes may give rise to downstream cost savings. A study with PGT-guided therapy in bipolar disorder found a decrease in hospitalizations, a shorter duration of hospitalization, and less use of emergency medical services, ultimately leading to potential overall cost savings to the healthcare system, as compared with non-PGT guided therapy.[79]

Involving patients in the treatment decision-making process can improve adherence, particularly when patient and provider expectations and responsibilities to each other are clearly established.[3] With a collaborative approach, patients

can take an active role in guiding their drug titrations. For example, a majority of adults with ADHD can identify when the effects of their medications are wearing off.[80] Providers can use this information to fine tune the drug titrations to improve symptom control over the course of the day.[80] Moreover, advances in information technology should allow both clinicians and patients to be partners in this individualized approach to drug dosing.[1] Information technology, for instance, electronic medical record systems, should assist in the collection and analysis of data from the real-world setting, which can then be used to inform clinical decision making for personalized medicine.[17]

Costs

Medication titration is associated with excess healthcare resource utilization and healthcare costs. One study from a nationwide panel of neurologists showed that, for patients utilizing antiepileptic drugs, periods of titration incurred higher healthcare resource utilization and costs compared with maintenance periods.[81] Similarly, an analysis of a large claims database found that for patients with major depressive disorder who initiated therapy with a serotonin reuptake inhibitor, those who underwent dose titration experienced significantly higher healthcare resource utilization and healthcare costs after 8 weeks of therapy compared with those who did not undergo titration.[82]

While PGT has the potential to reduce titration-associated cost, some important factors to consider for PGT are: who and when to test, which test to select, and how to interpret and use the test's results.[27,83] For certain conditions, providers may consider PGT to provide minimal clinical information, and, therefore, not worth the costs.[27,83] Another barrier facing more widespread utilization of PGT in the United States is that third party payer reimbursement is highly variable depending upon the plan, the type of testing, and the specific test.[83–86] Due to this, if PGT is not covered by insurance, it is not likely patients will pay out-of-pocket for the service, with a survey showing that almost half of patients would not pay any out-of-pocket costs for PGT.[87]

Titration can also lead to medication waste, as dose changes may require different prescriptions for different strengths and thus lead to leftover drug supply.[88,89] Further, insurance plan policies present a barrier to titration due to drug supply requirements. For example, the 30- or 90-day supply requirement for coverage of the prescription, despite titration occurring in shorter intervals, leads to an excess of medication being dispensed to the patient.[89,90] A complication of this excess supply, as observed with opioids and ADHD medications, is the potential for drug misuse or diversion.[91–94] Titration can also lead to prescription refill issues. There is the potential for delay in therapy when the up-titration quantity exceeds therapeutic quantity limits for lower doses. In addition, up-titration with an existing prescription, as instructed by a provider directly to a patient, presents challenges at the time of refill since, without knowledge of the up-titration, insurance will consider it an early fill and deny coverage.[95–98]

Excess costs due to healthcare utilization and prescriptions fills, and corresponding drug waste, represent opportunities for improvement in drug titration. Insurance companies should devise procedures and policies that support optimization of drug titration. Further, increased acceptance of telehealth could support healthcare visits specifically for titration, thus reducing associated healthcare costs of titration-related visits from both a health system perspective, as well as direct and indirect patient costs.

Summary

Drug titration is a form of personalized medicine, and many drugs in a variety of therapeutic areas require dose titration due to PK/PD and PGT parameters, to achieve specific therapeutic goals, and/or to decrease the risk of adverse effects. For some drugs, all of these factors may be interrelated, leading to the necessity of an individualized, patient-centered approach that blends together the art and science of drug titration. This is in contrast to the population-based approach of "one-size-fits-all" dosing, which may not be as equally safe and effective among all patients.

There is a paucity of real-world data on the effectiveness and safety of specific titration schedules among titrated medications, hence the varied approaches to titration and lack of titration consensus for many medications. The widespread

use of electronic medical records and integration of medical and pharmacy records provides a unique opportunity to consistently and accurately capture titration details in a standardized manner. In turn, such documentation will improve the coordination of care between providers and patients, and enable research that produces real-world evidence to minimize harms and maximize positive clinical outcomes among titrated medications.

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