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Review Article

Disquisition of Drug Dose Determinations to Effectuate Sustained Therapeutic Response in Patients: A Comprehensive Review

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ABSTRACT

According to the World Health Organisation, the Defined Daily Dose is the estimated daily maintenance dosage for a medication used for its primary indication in humans. Drug dose determination is extremely important for any drug. When a newly created, more precise dose plan differs considerably from the authorised label, it is crucial to assess the stage of proof needed to modify the label and clinical practice. Age has a significant influence on dose modification, as the acronym implies, because different age groups have different pharmacokinetic and pharmacodynamic characteristics. Furthermore, the measuring of body surface area is one of the most used methods for determining the dosage of chemotherapy medications. The clinical practice guidelines frequently base their recommended dosages on research that include both acute and severe cases of a particular ailment. For drugs acting on central nervous system, tapering of the dose is necessary. Starting such treatment at a low dose and gradually increasing it may reduce the likelihood of the side effects. This all-encompassing strategy emphasizes the value of customized medicine in contemporary clinical practice while promoting patient-centered care. This review article schemes about the various drug dosing considerations reliant on the demographic data, severity of the disease, as well as the individual patient response considering the resulting pharmacokinetics and pharmacodynamics.

Keywords: Drug Dosing, Medication Management, Pharmacodynamics, Pharmacokinetics, Therapeutic Index.

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INTRODUCTION

The patient's entire body weight is typically used to calculate drug dosages. For obese patients, this is frequently unsuitable, thus doctors may choose to use a different body size description when prescribing medication. The patient's clinical response and, if available, therapeutic drug monitoring must be carefully monitored (Morrish *et al.*, 2011). In order to tackle this issue, the Defined Daily Dose (DDD), an enigmatic unit of measurement, was developed. Precision dosing is a medicine therapy optimisation technique that optimises pharmacological features, disease state characteristics, and patient-specific aspects to maximise medication doses, which are essential for human health (Leff and Roberts, 1982). The therapeutic index, or the connection between a drug's therapeutic and toxic dose, is determined by the median Effective Dose (ED_{50}) and median Toxic Dosage (TD_{50}) (McCallum *et al.*, 2014).

One prevalent way of administering drugs is still through set strategies, where patients receive the same dose. Nevertheless, a patient's weight, age, genetics, coexisting conditions, and other variables might cause notable differences in their Pharmacokinetic (PK) and Pharmacodynamic (PD) reactions (Rowe *et al.*, 1998). Different aging-related conditions and the ageing process itself can affect how drugs are absorbed, distributed, metabolised, and excreted. Pharmaceutical pharmacodynamics explains how drugs alter the body. The number as well as affinity of target receptors at the location of the action, signal transmission, and homeostasis control all influence a drug's pharmacological impact (Conroy *et al.*, 2007). Researching and forecasting pharmacodynamic changes in the elderly is more difficult.

Intentional "on-target" effects that result in the intended therapeutic response as well as unintended "off-target" effects that lead to negative outcomes can both be influenced by PK and PD genes. The gender-based pharmacokinetics and pharmacodynamics that result from the most clinically asmissible changes in human body and organ functions, are outlined in this review article. Potential dosage ramifications or substitutes for

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medications that are commonly provided to this patient group are also discussed. There are suggestions made on how clinical drug development, drug authorization, and proper prescribing should take aging into account.

Importance of dosing

According to the WHO, the Defined Daily Dose is the estimated routine maintenance dosage for a medication utilised for its primary index in humans. Dosage has a critical role in diseases and/or drugs that can prolong life or lessen severe morbidity.

Precision dosing, sometimes highlighted to as individualised dosing, is a medication therapy optimisation approach that considers disease state characteristics such as the degree of mortality as well as morbidity, patient-specific elements such as gene variations and organ functions, and drug attributes such as Pharmacokinetic/Pharmacodynamic (PK/PD) variability and Narrow Therapeutic Index (NTI) (Polasek and Peck, 2024).

Considerations for dose adjustments for patients

Demographic data of the patient

In determining the dosage appropriate for a certain condition, factors such as gender, Body Surface Area (BSA) and Body Mass Index (BMI), and so forth of the patient are taken account of. Given that the pharmacokinetic and pharmacodynamic characteristics of different age groups vary, age, as the name implies, plays a significant influence in dosage modification (Smorenburg *et al.*, 2003).

Age

As a person ages, they may experience more health problems that require continuing care. It's good to realize that increased medication uses and body changes linked with aging can enhance the risks of harmful or hazardous interactions between drugs. Age-related changes also affect how the body absorbs and uses pharmaceutical products. One of them could be related to how quickly drugs in the digestive tract enter the systemic circulation (Source: FDA).

In contrast, age-based dosing has shown to be a reliable and secure method (Hernández-Boluda *et al.*, 2018).

How does paediatric's age affect dose determination?

Lack of pharmacokinetic studies makes it difficult to determine the right dosing for youngsters. Adult research cannot always be simply applied to children's dosages (Mahmood, 2022).

Pharmacokinetics- in paediatrics

Absorption: The balance of intestinal fluids as well as the permeability of the gastrointestinal tract alter during young age. The absorption of oral medications is impacted via variations in the pH of the stomach, which declines through infancy and reaches adult value ranges by the period the child's age is two years (Lubitz *et al.*, 1988).

Eg: Infants have a higher possibility of methaemoglobinaemia when topical anaesthetics is given (Conroy *et al.*, 2000).

Distribution: Over the course of childhood, the distribution volume changes along with changes in water as well as fat storage. Young children have a larger proportion of extracellular water, when they get older, their deposits of body fat rise. Because circulating plasma protein concentrations are lower in infants, protein binding is reduced (Smits *et al.*, 2012).

Eg: Lower peak concentrations and greater distribution of protein-bound medications, like cefazolin (Kandasamy *et al.*, 2013).

Age-based dose calculations formulas in Paediatrics:

1. **Young's rule:**

[Age / (Age + 12)] x Recommended Adult Dose = Paediatric Dose

2. **Dilling's rule:**

[Age (in years)/20] × Adult dose

3. **Fried's rule:**

Age (months)/150 × Adult dose = Dose for Infant

Metabolism: There is activity in the Cytochrome P450 (CYP) enzymes in the foetus. Almost all enzymes become more active during the first few months after birth, but more or less, like CYP3A7, are interchanged by some other enzymes, in this scenario CYP3A4. Although it is thought to take at least three years for metabolic processes like glucuronidation to reach full activity, their exact development is unknown (Dunne *et al.*, 2011).

Eg: High extraction ratio drugs like propranolol's first pass metabolism is affected due to the higher blood flow in infants.

Elimination: Compared to neonates, preterm newborns have slower-developing renal excretion routes. Glomerular filtration rates reach adult levels around the age of two.

There are often insufficient pharmacokinetic studies conducted on children of different ages. Because of this, figuring out the right dosage for a child may be difficult (Hines, 2013).

Pharmacokinetics-in geriatrics

Absorption: Age-related declines in gastric motility and production, first-pass metabolism, splanchnic blood flow, and small intestinal surface area are known to underlie these. Reduced ability to dissolve drugs, reduced enhanced absorption of high-clearance medicines and drug absorption, and reduced intake from prodrugs have been implicated (Drenth-van Maanen *et al.*, 2009).

Eg: Erythromycin and ketoconazole's decreased bioavailability (Wilkinson, 1997).

Distribution: The distribution of medications that are lipid-soluble increases, the distribution of medications that are water-soluble decreases, the unrestricted concentration of basic medications decreases, and the quantity of free drug increases in older adults due to reduced total body water, a higher percentage of body fat, and a lower lean body mass, elevated α-I-acid glycoprotein degree, and malnourishment and proteinuria resulting in decreased albumin levels (hypoalbuminemia).

Eg: Drug toxicity is seen with acenocoumarol (Matsushita *et al.*, 2012).

Metabolism: Blood flow and mass in the liver are reduced, activity of the cytochrome P450 enzyme is decreased, and cytochrome P450 hepatic enzyme competition is exacerbated by liver disease, the typical aging-related physiological effects on the liver, and polypharmacy.

Eg: First pass effects of prodrugs are decreased (Brown-Borg *et al.*, 1996).

Elimination: Reduced Glomerular filtration rate and renal blood flow are the results of declining renal function and renal disease in the elderly.

Eg: Toxicology results from gentamicin buildup in plasma.

First-pass metabolism

The impact of first-pass metabolism goes down with age, most probably as a result of a decline in CYP and liver bulk and blood flow and other biotransformation activities of enzymes, including flavine monooxygenases and Uridine Diphosphate (UDP) glucuronosyl transferases. As a consequence, certain medications, particularly those with a limited therapeutic index, ought to be started at a minimal dosage. The inhibitors of the angiotensin-converting enzymes perindopril and enalapril are two examples of pro-drugs whose first-pass activation may be reduced as a result of decreasing first-pass metabolism. This could potentially result in lower systemic concentrations of the active drug ingredient (Park *et al.*, 2007).

Gender

It has been demonstrated that a female increases the chance of experiencing clinically significant adverse medication responses than a male. Though few medications are dosed according to body weight, men typically weigh more than women. For the majority of medications, both metrics are based on body weight, irrespective of gender (Baraona *et al.*, 2001).

The gender-based drug determination is generally due to two prospects which includes anatomical differences and pharmacological responses between the male and female.

Based on the anatomic composition of the body

Men and women make up different proportions anatomically (Table 1). Males possess greater lean mass, while the fat mass of women is higher. In women, adipose tissue usually builds up around the hips and thighs, but in men, it tends to build up around the trunk and abdomen (Caballeria *et al.*, 1989).

Based on difference in pharmacological responses

Pharmacokinetic parameters in Male and Female (Table 2).

Pharmacodynamic Parameters in Male and Female

The study of pharmacodynamics focuses on the pharmacological way of action, which includes the body's physiological and metabolic impacts as well as the connection between drug levels and the size and rate of elicitation (Park *et al.*, 2021).

For example, women are more responsive to the interactions between tricyclic antidepressants and Selective Serotonin Reuptake Inhibitors (SSRIs) than men are. Women receiving SSRI therapy may produce more tryptophan and less cortisol. Tricyclic antidepressants, however, are more effective for men than SSRIs (Kornstein *et al.*, 2000).

Women respond more strongly to beta blockers, especially metoprolol, in terms of pharmacodynamics. It's because women have larger drug concentrations in their plasma.

Body Weight and Body Mass Index (BMI)

BMI has a stronger correlation with other metabolic and disease outcomes than these more accurate measures of body fatness.

Paediatrics

The dosage for paediatric patients is calculated using Clark's rule, which takes into account the known weight of the patient and the adult dosage of the drug.

(Weight divided by 150 lbs.) x Adult Dose = Pediatric Dosage

(Weight divided by 68 kg) x Adult Dose = Pediatric Dosage (Elias *et al.*, 2005)

For instance, the prescription for methotrexate for young patients suffering with Acute Lymphoblastic Leukemia (ALL) was

Table 1: Disparities between male and female anatomy (Huttunen *et al.*, 2007).

Parameter	Disparity
Body Weight (kg)	Adult male > Pregnant female > Adult female
Body Length (cm)	Adult male > Pregnant female = Adult female
Body Surface Area (cm^2)	Adult male > Pregnant female > Adult female

Table 2: Pharmacokinetic parameter differences between males and women (Masanja *et al.*, 2013).

Parameters	Male	Female
Absorption (Elias *et al.*, 2005) Drug-specific factors determine a drug's absorption rate and extent. a. Gastric enzymes b. Gastric fluid flow and acid production.	a. Males have higher gastric alcohol dehydrogenase activity than females do b. Higher	a. Compared to Men; Women are less likely to alcohol toxic threshold and get alcoholic liver damage more quickly b. lower respectively compared with men.
Distribution Differences between these characteristics depending on a person's gender could clarify alterations in the drug's concentration (Yamashita *et al.*, 2012). a. Resting blood flow as a percentage of carbon monoxide (Masanja *et al.*, 2013). b. Body mass index (Yamashita *et al.*, 2012).	. Skeletal muscle (greater in men) b. Male > Female	a. Adipose tissue (greater in women) b. Female < Male
Metabolism Gender-related pharmacokinetic activity is mostly determined by variations in hepatic enzymes. a. Activity of CYP3A4 and CYP2D6 (Rhodin *et al.*, 2009). b. Basal Metabolic Rates (BMR) (Chen *et al.*, 2023).	a. Male < Female b. Men typically have a greater BMR than women across all age groups.	a. Higher in females b. Because women have a lesser skeletal muscle component, their lean body mass is reduced, which is reflected in their lower BMR per unit body surface area.
Excretion Drug inactivation is caused by two procedures, either metabolism or elimination, independently or in combination. a. Renal blood flow b. Pulmonary function	a. Increased renal elimination b. Increased pulmonary elimination	a. Male > Female b. Male > Female

determined by the patient's BSA. Jonsson *et al.* (2011) created a population-based pharmacokinetic model for kids with ALL. The findings demonstrated that methotrexate based on weight dosage could improve outcomes and produce more predictable pharmacokinetics in children with ALL. A common surgical prophylactic prescription is for cephalosporins. The dose needs to be raised since obese persons have higher clearance rates. In order to provide adequate exposure, the suggested dosage of 1 g has been raised to 2 g for obese patients, and it may need to be given more regularly (Huttunen *et al.*, 2007).

Lean and obese patients

Weight-based dosing may or may not be applicable depending on clinical indications, physiological considerations, and pharmaceutical kinds (Masanja *et al.*, 2013).

For instance, Immunoglobulin G (IgG) effectiveness was examined in lean and obese patients receiving replacement or immunomodulatory therapy by Hodkinson *et al.* (Yamashita *et al.*, 2012) Obese patients had greater serum IgG levels increases in comparison to lean ones. Reducing the dosage for some obese individuals getting IgG for immunomodulation showed promise; this result in cost savings without sacrificing therapeutic performance. When edoxaban 60 mg is administered once daily to Japanese patients with nonvalvular atrial fibrillation, the frequency of all bleeding episodes was roughly twice as high in patients ≤60 kg as in patients >60 kg. This suggested that dose reduction is necessary in underweight patients (≤60 kg) (Rhodin *et al.*, 2009).

Body surface area

The most popular approach for determining the dosage of chemotherapeutic medications is body surface area (Chen *et al.*, 2023). Early studies on chemotherapy discovered that when doses were according to body surface area instead of just body weight, the side effects of these treatments for cancer were far more consistent between subjects.

Paediatrics

The primary foundation for medication dose should be body surface area since the pace of drug redistribution or metabolism is correlated with metabolic pace, which consequently represents heat losses that are normally in proportion to the surface area for any heated object (Green and Duffull, 2003).

Child dose = Child's BSA / Average adult's BSA × adult's dose (Udy *et al.*, 2010a)

Adults: Chemotherapeutic doses have historically been determined by body surface area. Several older medications, such as doxorubicin, paclitaxel, and cyclophosphamide, were "capped" (usually at 2 m^2), which may have led to sub-therapeutic treatment. According to recent guidelines, body surface area should be calculated using total body weight until further study is conducted, providing there is a valid cause to lower the dose, such as renal disease (Udy *et al.*, 2010b).

Severity of the disease

Clinical practice recommendations often draw their suggested dosages towards studies involving acute and severe instances of a given condition.

Chronic conditions

The use of long-term medication to manage symptoms and halt the course of chronic conditions is growing. The likelihood of adverse outcomes is higher when medication dosages are high. Even in cases of mild disease, people frequently disregard the lowest suggested medicine doses, most likely due to concerns about sub-therapeutic dosing (The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002).

Particularly in primary care as well as for sustaining abatement, low dosages of medication have become more and more common in chronic diseases. For example, thiazides given for hypertension (12.5 mg versus 50 mg daily) (Pitt *et al.*, 1999), spironolactone given for heart failure (25 mg versus 200 mg daily) (Holt *et al.*, 2001), inhaled fluticasone provided for asthma (175 mg versus 500 mg daily) (Wassenberg *et al.*, 2005), prednisolone given for rheumatoid arthritis (5 mg up to 25 mg daily), aspirin given for cardiovascular disease (75 mg versus up to 650 mg daily) (Campbell *et al.*, 2007), and haloperidol for schizophrenia (50 mg versus 200 mg monthly) (Chakrabarti and Kandror, 2009) all demonstrate a good degree of efficacy at much lower doses.

It is best to "start low and go slow" while treating mild complications in primary care to prevent going over the recommended dose, especially when using medications like digoxin that have a limited therapeutic window (Cockcroft and Gault, 1976).

Acute conditions

In cases of acute, severe illness, high dosages are frequently lowered for upkeep. For example, up to 160 mg of frusemide can be taken per day to treat acute pulmonary oedema; however, the dosage should be reduced to 20 to 40 mg per day in order to avoid recurrence. Likewise, the first daily dosages of are usually replaced with maintenance dosages such as 600 mg of clopidogrel, 3 mg of colchicine, and 1200 mg of amiodarone, respectively.

Drug dose determination in acute and chronic kidney disease patients

It is a normal practice to alter drug dosages for individuals suffering from acute or chronic kidney illness. In particular, the parameter that directs dosage adjustment is Glomerular Filtration Rate (GFR). It is determined using the Creatinine Clearance (CrCl).

Cockcroft and Gault rule
Clcr (mL/min) = (140-age (years) × weight (kg) × 0.85 [female]) / (Scr (mg/dL) × 72) *(Matzke et al., 2011)*

Numerous organ systems may be impacted by Chronic Kidney Disease (CKD) and Acute Kidney Injury (AKI), and these physiological modifications have been linked to symbolic changes in the PK and PD of numerous medications (Son *et al.*, 2020).

Adjusting dosages for CKD patients

Patients with chronic renal disease typically don't need their loading dosages changed (Table 3). According to published guidelines, maintenance dosing modifications should involve either lowering the dosage, increasing the interval between doses, or doing both (Jin *et al.*, 2015). Dose reduction method keeps more stable levels of drugs, although toxicities are more likely if the time between doses is too short to permit clearance of drugs. Extending the interval has been linked to a decreased risk of toxicities but an increased likelihood of medication concentrations below therapeutic levels, particularly near the conclusion of the dosage gap (Bennett *et al.*, 1983).

Drug dosage modifications in patients with AKI

AKI and Multisystem Organ Failure/Multiorgan Dysfunction Syndrome (MSOF/MODS) patients are based on the concepts of drug dose regimen adjustment for usage in CKD patients. Due to the maintenance of nonrenal clearance for certain medications, including ceftizoxime, imipenem, and vancomycin, and the propensity to achieve a positive fluid balance in the initial

Table 3: Drug dosage adjustment based on GFR in patients with kidney disease.

Drugs used in patients with kidney disease	Standard dosage	GFR-based dose modification (% of standard dosage) (mL/min/1.73 m2) >50 10-50 <10
ACE inhibitors: Captopril Beta blockers: Atenolol	25 mg for every 8 hr 5 to 100 mg every day	100% 75% 50% 100% 50% 25%
	Hypoglycaemic agents	
Acarbose Metformin	Maximum of 50 to 100 mg three times a day 500 mg twice a day	Avoid Avoid (if serum creatinine level >1.5 mg/dL in men and >1.4 mg/dL in women and patients >80 years of age)
	Antimicrobial agents	
Fluconazole Meropenem	200 to 400 mg once a day 1 to 2 g for every 8 hr	100% 50% 50% 100% 50% 50%
	Other medications	
Atorvastatin Ranitidine	10 mg daily Maximum dosage: 80 mg daily 150 to 300 mg at bedtime	No adjustment needed 75% 50% 25%

phases of acute kidney injury, many medications, particularly antibacterial substances, ought to be started on typical or nearly standard dose schedules (Hou *et al.*, 1983).

Demographic data as well as severity of the disease

Antibiotic dosing

Most off-label medications in primary care are for antibiotics, which are among the most often prescribed medications for kids of all ages. Off-label medication usage in children is undesirable and may expose them to unidentified hazards.

When comparing the dosage for each antibiotic to that for adults and pediatrics (Table 4), we may observe a progressive change. It is necessary to strengthen the pharmacokinetic, pharmacodynamic, and clinical data pertaining to the dosing of pediatric antibiotics, especially with regard to total dosages and age/weight dosing bands (Moore *et al.*, 1984).

Levothyroxine initial dosage and dose adjustment during therapy

The initial dosage of levothyroxine that a patient need is determined by three primary elements:

1) Lean body mass or the patient's body weight,

2) the degree of residual thyroid function retained by the patient, and

3) the desired level of Thyroid-Stimulating Hormone (TSH) or thyrotropin that needs to be reached during treatment (Jonklaas *et al.*, 2014).

For instance, small doses of 25-50 μg might be needed in a patient with less moderate to moderate subclinical illness, where the treatment may be supporting endogenous function. When endogenous thyroid function is minimal, higher dosages of 88-175 μg might be required. One dose increases or decrease, such as from 100 to 112 μg or from 175 to 150 μg, can correct slightly off-range TSH readings (Elfenbein *et al.*, 2016).

Fixed dose range

Some of the drugs have a fixed range of dose for all patients irrespective of their age, gender or severity of the disease.

Some of the examples include:

Ondansetron [Available fixed dose range: 4 mg-24 mg orally and 2 mg/mL intravenous (iv)]- Dosage depends on the cause and mode of administration. However, the maximum suggested individual dose is 16 mg per IV injection due to the potential for arrhythmias and corrected QT interval (QTc) prolongation. There is no need to change the dosage for individuals with impaired kidney function who are taking their medications orally or intravenously. For patients with severe hepatic impairment, the maximum daily dosage is reduced to 8 mg IV or 8 mg oral. A

paediatric weight-based dosage of up to 16 mg per dose, or 0.15 mg/kg, is prescribed (Rapp *et al.*, 2015).

Pantoprazole [Available fixed dose range: 20-40 mg orally and 40 mg/vial IV]- The suggested dosage for each of these regimens is 40 mg twice a day of pantoprazole. It is advised to administer an 80 mg loading dosage and then an 8 mg infusion per hour to avoid peptic ulcer rebleeding. The suggested daily dosage for Non-Steroidal Anti-Inflammatory Drug (NSAID)- induced ulcers is 20-40 mg orally (Turedi *et al.*, 2017).

Statins

Paediatric Considerations

Moderate-to high-intensity statin medication is advised for paediatric patients with hereditary hypercholesterolemia (Luirink *et al.*, 2019).

Geriatric Considerations

When discussing the possible advantages of preventative therapies with patients who are older than 75, the practitioner and patient should take into account the patient's comorbidities and expected lifespan.

Patients with Renal Impairment

A network meta-analysis indicated that high-dose atorvastatin and fluvastatin 20 mg/ezetimibe 10 mg effectively avoided eGFR decline and proteinuria. When using alternative statins, individuals with stage 4 CKD (creatinine clearance less than 30 mL/min) must adjust their dosage (Esmeijer *et al.*, 2019).

Individual patient response/tolerance

This method of dosage determination is especially used when the drug's effects cannot be directly monitored and when there

Table 4: Dose of few antibiotics in children and in adults (as per BNF).

Antibiotic	Dose for Paediatrics	Dose for adults
Amoxicillin	(For the treatment of susceptible infections) 1 to 11 months- 125 mg TDS (thrice a day) 1 to 4 years- 250 mg TDS 5 to 11 years- 500 mg thrice a day 12 to 17 years- 500 mg- 1 g thrice a day	(For the treatment of susceptible infections) 500 mg- 1 g every 8 hr
Ceftriaxone	(For the treatment of pneumonia) <15 days- 20-50 mg/kg OD (once a day) IV (intravenous) 15 to 28 days- 50-80 mg/kg OD IV 1 month to 11 years- 50-80 mg/kg OD im (intramuscular)/IV 9-11 years- 1000-2000 mg/day im/IV 12-17 years- 1000-2000 mg/day im/IV	(For the treatment of pneumonia) 1-2 g OD im/IV
Ciprofloxacin	(For the prevention of meningococcal meningitis recurrence) 1 month to 4 years- 30 mg/kg for 1 dose 5 to 11 years- 250 mg for 1 dose 12 to 17 years- 500 mg for 1 dose.	(For the prevention of recurrence of meningococcal meningitis) 500 mg given for 1 dose.
Doxycycline	(For the management of susceptible infections) For children aged 12 to 17, take 200 mg OD in 1-2 divided doses for one day, followed by 100 mg daily for maintenance.	(For the treatment of susceptible infections) 200 mg per day for a day in 1-2 divided doses, followed by 100 mg per day for maintenance.
Metronidazole	(For the treatment of anaerobic infections) 7.5 mg/kg every 12 hr for one month, typically for seven days of treatment 2 months-11 years: 7.5 mg/kg every 8 hr (400 mg maximum dose), typically for 7 days 12-17 years- 400 mg every 8 hr usually treated for 7 days.	(For the treatment of anaerobic infections) 400 mg every 8 hr usually treated for 7 days, alternatively 500 mg every 8 hr usually treated for 7 days.

Table 5: Drugs used in epilepsy therapy (Source: BNF).

Drug	Child dose	Adult dose
Sodium valproate	Initially, 10-15 mg/kg daily in 1-2 divided doses (maximum per dosage of 600 mg) for students aged 1 month to 11 years; maintenance: 25-30 mg/kg daily in 2 divided doses Ages 12 to 17: 600 mg daily in two divided doses at first, then 150-300 mg every three days; maintenance: 1-2 g daily in two divided doses; daily maximum: 2.5 g.	600 mg daily in two divided doses at first, then 150-300 mg every three days; maintenance of 1-2 g daily, or maintenance of 20-30 mg/kg daily; maximum of 2.5 g daily.
Carbamazepine	1 month to 11 years: 5 mg/kg OD at first, then 2.5-5 mg/kg every 3-7 Days as needed 12-17 years old: 100-200 mg at first 1-2 times day, followed by a gradual increase to 200-400 mg 2-3 times daily, and if required, up to 1.8 g daily.	100-200 mg once or twice daily at first, then 100-200 mg every two weeks, and if needed, up to 1.6-2 g daily in divided doses.
Levetiracetam	16 to 17-year-olds: start with 250 mg OD for a week, then raise to 250 mg BD, then increase in steps of 250 mg BD (adjusted based on response), increasing the dosage every two weeks.	Starting at 250 mg OD for one to two weeks, then increasing to 250 mg BD, and then increasing in increments of 250 mg BD (adjusted based on response), with dose increases occurring every two weeks.

is a greater challenge to make the drug reach the place of action. This can be seen in the cases of Central Nervous System (CNS) conditions. For a drug to cross Blood Brain Barrier (BBB), the factors affecting are: - Lipophilicity, molecular weight, molecular charge, chemical structure and chemical conformation (Arnold *et al*., 2011).

Dose modifications for patients with epilepsy

Changes in medication are often required due to the ineffectiveness or intolerability of the original course of treatment. Real-world epilepsy treatment is very customized, and when it comes to the commencement and optimization of ASM, clinical settings may diverge from clinical trials that were randomized studies, especially when it comes to patients undergoing polytherapy ("Guidelines for Epidemiologic Studies on Epilepsy," 1993).

Why high starting doses when provided to an epileptic person is dangerous and not recommended?

Hypersensitivity reactions mediated by the immune system, including Toxic Epidermal Necrolysis (TEN), Stevens-Johnson Syndrome (SJS), and Drug-Related rash with Eosinophilia and Systemic Symptoms (DRESS), are rare but potentially fatal idiosyncratic side effects associated with ASMs high doses at first (Yawalkar *et al*., 2000).

The likelihood of a serious cutaneous adverse response is boosted by fast rates of titration with a number of ASMs, such as phenytoin, lamotrigine, and carbamazepine.

In elderly patients

Titration is crucial for senior individuals as well because of the high prevalence of coexisting diseases (such as diabetes, cardiovascular disease), concurrent drug use, and aging-related physiological changes in metabolism that increase the risk of side effects and possible drug interactions. For instance, ASMs that increase or decrease Permeability glycoprotein (P-gp) efflux or hepatic cytochrome P450 enzymes may interact with oral anticoagulant and antiplatelet medication metabolism, raising the risk of thromboembolic or bleeding events (Guégan *et al*., 2006).

PK and PD factors

Many ASMs, especially the older ones, function as CYP enzyme inducers or inhibitors (valproate, for example) and may cause pharmacokinetic drug-drug interactions when used with other medications (Acton *et al*., 2020). Titration needs to be strictly watched when switching from an ASM monotherapy that induces or inhibits an enzyme to another ASM that is vulnerable to its effects.

Adjusting the dosage of the other medication(s) and implementing flexible dose titration may assist prevent drug toxicity when patients are switching from monotherapy to another or include an additional therapy. From Table 5, it is seen that CNS drug doses are gradually increased since sudden higher doses might lead to various side effects.

Tapering of dose

Patient preference is becoming more and more important in a time when shared decision-making and paternalism are declining.

It is true that patients frequently stop taking their medications suddenly, and that they may do so more frequently if their doctors disregard their choices. Discontinuing antipsychotic medication suddenly is more likely to cause withdrawal symptoms and a relapse.

Therefore, more gradual tapering could lower the likelihood of relapsing following cessation of antipsychotics. There's increasing proof that the effects of antipsychotic exposure can last for months or even years after the drug is stopped, as evidenced by study on animals, patient observations of tardy dyskinesia, as well as the relapse clusters during this time frame following antipsychotic withdrawal (Perucca, 1987).

CONCLUSION

This review of the weight-based dosage method in medication administration will advance our understanding of safety, efficacy, and pharmacoeconomics and guarantee that clinicians are knowledgeable about the dosage and administration of prescribed medications. Healthcare professionals must be aware of these drug dose determination methods for any drug. In conclusion, achieving a sustained therapeutic response in patients through precise drug dose determinations stands as a pivotal goal in contemporary healthcare. By tailoring drug dosages to each patient's requirements, we can maximise effectiveness, reduce side effects, and improve patient outcomes and quality of life. This comprehensive approach fosters patient-centred care and underscores the importance of personalized medicine in modern clinical practice. Clinical research, technological advancements, and interdisciplinary collaboration will be essential in refining dosage determination strategies and advancing the frontier of therapeutic precision, ultimately empowering clinicians to deliver the most effective treatments designed to each patient's unique physiology and condition.

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Not applicable.

ABBREVIATIONS

DDD: Defined Daily Dose; **PK:** Pharmacokinetics; **PD:** Pharmacodynamics; **BSA:** Body Surface Area; **BMI:** Body Mass Index; **CYP:** Cytochrome P450; **WHO:** World Health Organization; **ED_{50}:** Median Effective Dose; **TD_{50}:** Median Toxic Dose; **NTI:** Narrow Therapeutic Index; **GFR:** Glomerular Filtration Rate; **CrCl:** Creatinine Clearance; **CKD:** Chronic Kidney Disease; **AKI:** Acute Kidney Injury; **MSOF:** Multiple System Organ Failure; **MODS:** Multiple Organ Dysfunction Syndrome; **TSH:** Thyroid-Stimulating Hormone; **NSAID:** Non-Steroidal Anti-Inflammatory Drug; **ALL:** Acute Lymphoblastic Leukemia; **IgG:** Immunoglobulin G; **CNS:** Central Nervous System; **BBB:** Blood-Brain Barrier; **ASM:** Anti-Seizure Medication; **TEN:** Toxic Epidermal Necrolysis; **SJS:** Stevens-Johnson Syndrome; **DRESS:** Drug Rash with Eosinophilia and Systemic Symptoms; **P-gp:** Permeability Glycoprotein; **ACE:** Angiotensin-Converting Enzyme; **SSRIs:** Selective Serotonin Reuptake Inhibitors; **BMR:** Basal Metabolic Rate; **BNF:** British National Formulary; **IV:** Intravenous; **IM:** Intramuscular; **OD:** Once Daily; **BD:** Twice Daily; **TDS:** Three Times Daily.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [PC], [MSJ] and [SR]. The first draft and methodology of the manuscript was written by [PC]. All authors read and approved the final manuscript. [JM] reviewed and edited the article.

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