VOLUME 3, ISSUE 1 , March 2023

هيئة الدواء المصرية
الإدارة المركزية للرعاية الصيدلية
الإدارة العامة للممارسات الدوائية و الصيدلية

NOHARMe Newsletter

"Avoid errors… Optimize care"

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Inside this Issue

Close Insights on NOHARMe Reports in 2022

General Administration of Drug Utilization & Pharmacy Practice **is pleased to exchange the experiences among clinical pharmacists by publishing a new issue of its medication safety newsletter.**

NOHARMe newsletter was launched to provide information on the safe and effective use of medications and to share knowledge on the patterns of medication errors and drug therapy problems reported to the NOHARMe system.

In appreciation for their efforts, we would like to thank all clinical pharmacists who have been keen on documenting their interventions and reporting them to the NOHARMe.

NOHARMe "National Office for Handling And Reduction of Medication error" **is a system for gathering, analyzing, and sharing data on medication errors and drug therapy problems. It aims to raise awareness among healthcare providers on the most frequent and serious errors while handling drug products and to build a national pool of data that can be used to educate practitioners to avoid the recurrences of further errors and hence enhance good pharmacy practice NOHARMe aims to promote safer healthcare by implementing preventive strategies and system safeguards.**

NOHARMe system **records two types of clinical pharmacy interventions related to pharmacotherapy:**

- **Drug Therapy Problems .**
- **Medication Errors.**

Drug Therapy Problems **are problems discovered during appropriateness reviews conducted on patients' medical therapy; the reviewer decides there are problems with pharmacotherapy: if, for example, it is not following the latest guidelines, or when they simply have a different opinion than the prescriber.**

Medication errors **are errors that occur while implementing a patient's therapeutic plan that has already been discussed and approved by clinicians. Medication errors are classified according to the stages of medication use, e.g. medication preparation, administration ... etc.; also, they are given severity ratings based on: whether they have reached a patient; whether they have caused harm; and the type of harm they caused. It takes clinical knowledge and drug use expertise to review a patient's therapeutic plan and discover Drug Therapy Problems; on the contrary, Medication Errors can be documented by anyone including patients.**

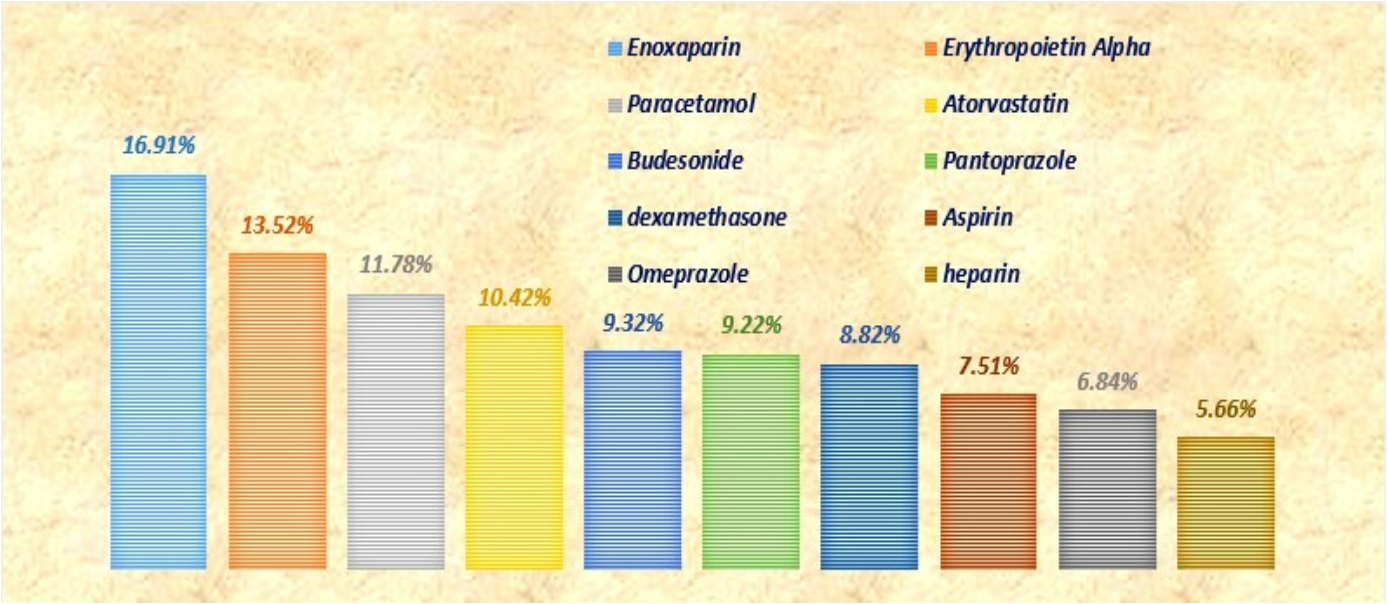
Analyzing and Interpreting NOHARMe Data Generated in 2022

Overall Reports

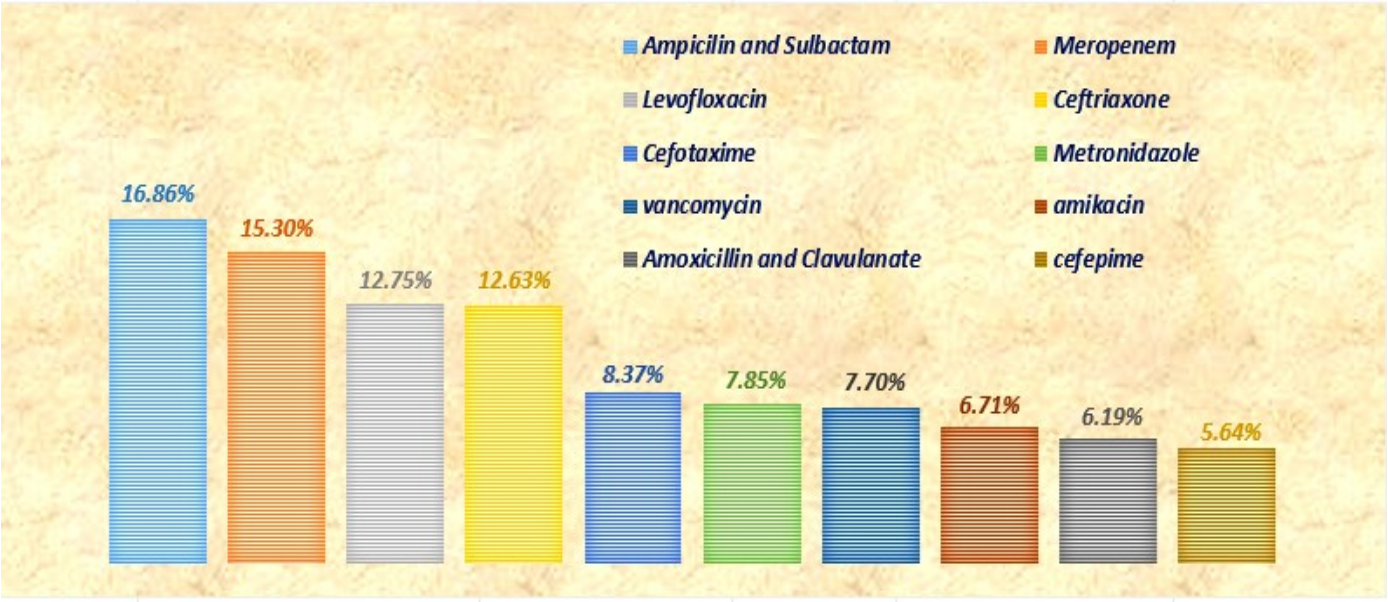
After validation of NOHARMe reports generated in 2022, it showed that 43.7 % of them have been labeled as drug therapy problems "DTPs" only, 3.8 % have been labeled as medication errors "MEs" only, and 52.5 % have been labeled as drug therapy problems that are also medication errors.

After report analysis, it was found that antimicrobials dominate the received reports. Therefore, the reports were categorized into two major groups: Antimicrobial-related and non-antimicrobial-related. Further analysis showed that Ampicillin/Sulbactam and Meropenem were the most reported antimicrobials with MEs or DTPs. As for the non-antimicrobial side, Enoxaparin and Erythropoietin Alpha were the top reported medications.

Top 10 Reported Drugs *(excluding antimicrobials)*



Top 10 Reported Antimicrobials



Erythropoiesis-Stimulating Agents (ESAs)

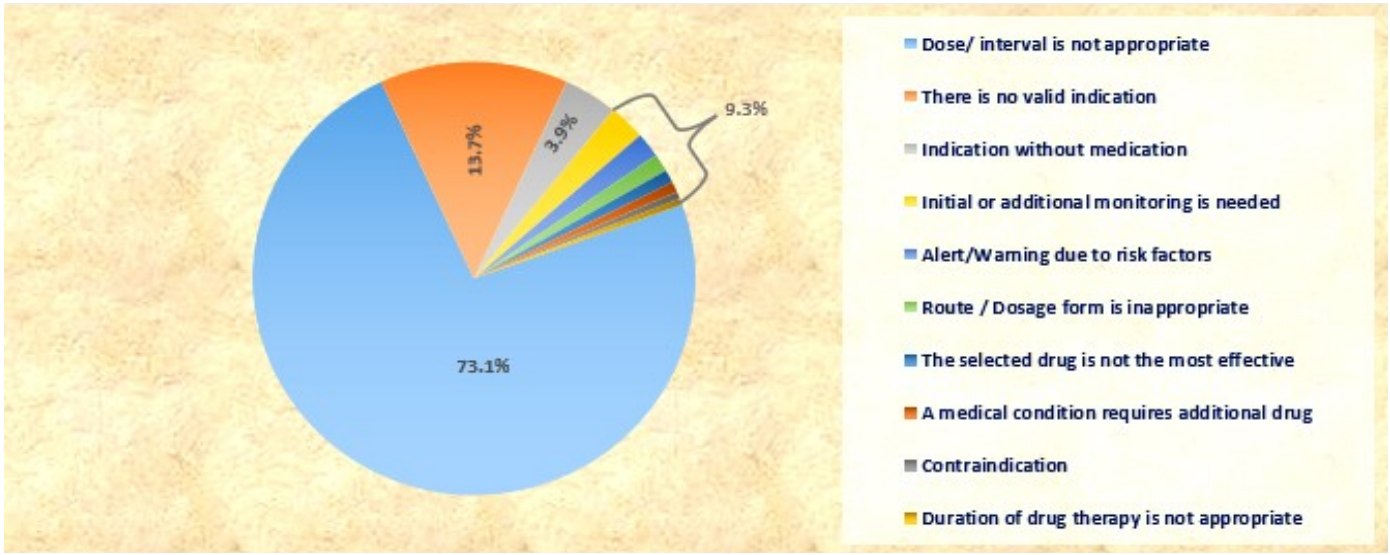
Introduction

Endogenous erythropoietin (EPO) is a vital glycoprotein hormone produced by the kidneys to stimulate the bone marrow to produce red blood cells (RBCs). In patients with chronic kidney disease (CKD), the damage to the kidneys limits the production of endogenous EPO. Since Erythropoiesis-stimulating agents (ESAs) are the recombinant derivatives of EPO, they are indicated for instances when RBC production is impaired, such as anemia secondary to CKD.

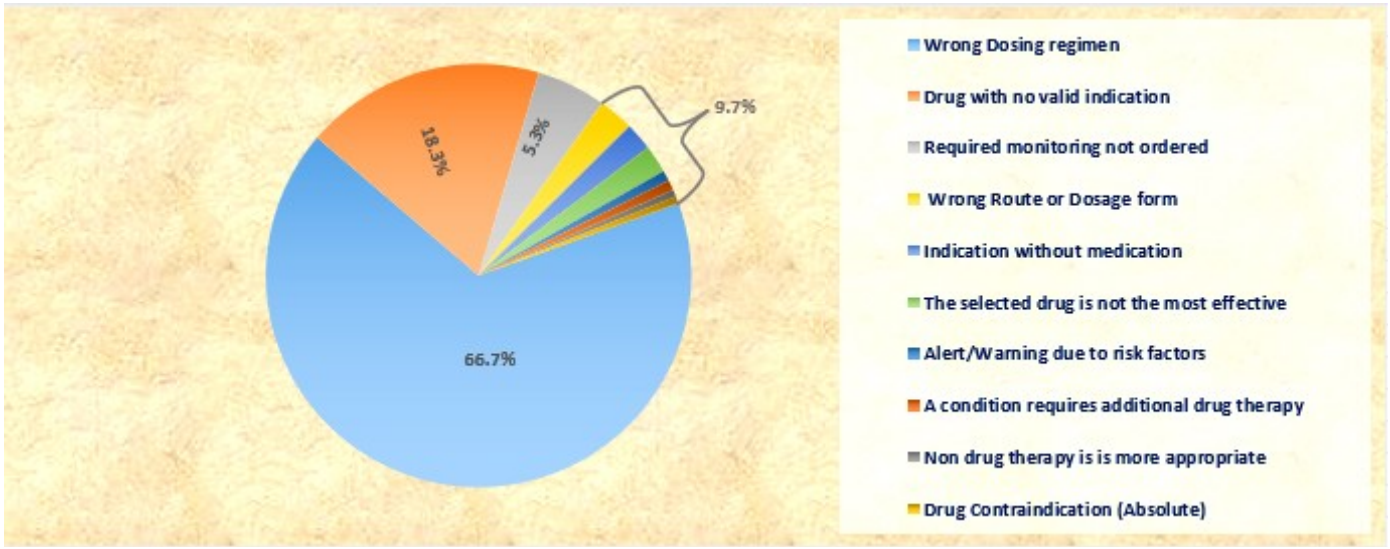
Types of Erythropoiesis-Stimulating Agents (ESAs)

	Epoetin Alfa	Epoetin Beta	Methoxy polyethylene glycol-epoetin beta	Darbepoetin alfa
Available Strengths	2000 I.U/ml; 2000 I.U/0.5ml; 4000 I.U /0.4ml; 10000 I.U/ml; 40000 I.U/ml	2000 I.U./0.3ml ; 3000 I.U./0.3ml ; 4000 I.U./0.3ml ; 5000 I.U./0.3ml	50 mcg/0.3ml; 75 mcg/0.3ml; 100 mcg/0.3ml	10 mcg/0.4ml; 20 mcg/0.5ml; 30 mcg/0.3ml; 40 mcg/0.4ml; 60 mcg/0.3ml; 100 mcg/0.5ml; 150 mcg/0.3ml; 300 mcg/0.6ml

Types of Drug Therapy Problems Associated with ESA



Types of the Medication Errors Associated with ESA



When it comes to the appropriate use of ESAs, the dosing regimen was found to be the main concern for practitioners, with an incidence exceeding 66% of the total reported MEs. To a lesser extent, ESAs were prescribed without a valid indication in 18% of the reports. Moreover, despite the lower incidence rate, it was noted that there is some concern related to the appropriate ESAs route of administration between dialysis and non-dialysis patients, which we plan to address within this issue.

ESAs Dosing Chart

Indication: Anemia due to Chronic Kidney Disease (CKD)

Epoetin Alfa	Initial dose (Dialysis)	IV, SC: 20 to 50 units/kg 3 times weekly; in some patients with lower initial Hb levels (e.g., <8 g/dL), an initial dose of up to 100 units/kg 3 times weekly may be considered.
	Initial dose (No Dialysis)	IV, SC (preferred) 50 to 100 units/kg every 1 to 2 weeks; typical initial regimens include 4,000 to 10,000 units once weekly or 10,000 to 20,000 units every other week.
Epoetin Beta	Initial dose (Dialysis)	IV (preferred) 40 units/kg 3 times weekly. After 4 weeks, may increase dose to 80 units/kg 3 times weekly based on Hb response. May increase dose every 4 weeks by 20 units/kg/week if necessary (max: 720 units/kg/week).
	Initial dose (No Dialysis)	SC (preferred) 60 units/kg/week, administered as a single dose or in 3 to 7 divided doses. If Hb response is <0.25 g/dL weekly, may increase dose every 4 weeks by 60 units/kg/ week (max.: 720 units/kg/week).
	Maintenance	IV, SC: After reaching Hb target, reduce weekly dose to half of the previously administered dose and titrate every 1 to 2 weeks as needed until stable Hb response is achieved. (The total weekly SC dose may be administered once weekly or in divided doses administered 3 times weekly or once daily for 7 days) If Hb is stable with once weekly SC dosing, the interval can be extended to once every 2 weeks (dose increase may be required).
Methoxy Polyethylene Glycol-Epoetin Beta	Initial dose (Dialysis)	For patients not currently on ESA: IV, SC: 0.6 mcg/kg once every 2 weeks.
	Initial dose (No Dialysis)	For patients not currently on ESA: IV, SC (preferred): 0.6 mcg/kg once every 2 weeks. Some experts initiate at 0.6 mcg/kg once every 2 to 4 weeks based on patient-specific factors (eg, baseline Hb).
	Initial dose (Conversion)	For Patients converting from Epoetin Alfa or Darbepoetin Alfa (Check conversion table below) IV, SC: Based on total weekly ESA dose at the time of conversion, provided Hb has been stabilized
Darbepoetin Alfa	Initial dose (Dialysis)	For patients not currently on ESA: IV, SC: 0.45 mcg/kg once weekly or 0.75 mcg/kg once/2 weeks
	Initial dose (No Dialysis)	For patients not currently on ESA: IV, SC (preferred): 0.45 mcg/kg once every 2 to 4 weeks.
	Initial dose (Conversion)	For Patients converting from Epoetin Alfa or Darbepoetin Alfa (Check conversion table below) The dose conversion in the table does not accurately estimate once-monthly doses of darbepoetin alfa in patients with CKD not on dialysis.

Conversion between ESAs (For Anemia in CKD)

From Epoetin Alpha	to Methoxy Polyethylene Glycol-Epoetin Beta
< 8,000 units/week	120 mcg once monthly or 60 mcg once every 2 weeks.
8,000 to 16,000 units/week	200 mcg once monthly or 100 mcg once every 2 weeks.
> 16,000 units/week	360 mcg once monthly or 180 mcg once every 2 weeks.

From Darbepoetin Alfa	to Methoxy Polyethylene Glycol-Epoetin Beta
< 40 mcg/week	120 mcg once monthly or 60 mcg once every 2 weeks.
40 to 80 mcg/week	200 mcg once monthly or 100 mcg once every 2 weeks.
> 80 mcg/week	360 mcg once monthly or 180 mcg once every 2 weeks.

From Epoetin Alfa (Total Weekly Dose)		To Darbepoetin Alfa
If current dose 2 to 3 times/ week	If current dose is once weekly	Once weekly if Epoetin alfa 2 to 3 times weekly Every 2 weeks if Epoetin alfa once weekly
≤ 2,499 units/week	≤ 1,249 units/week	6.25 mcg per dose
2,500 to 4,999 units/week	1,250 to 2,499 units/week	12.5 mcg per dose
5,000 to 10,999 units/week	2,500 to 5,499 units/week	25 mcg per dose
11,000 to 17,999 units/week	5,500 to 8,999 units/week	40 mcg per dose
18,000 to 33,999 units/week	9,000 to 16,999 units/week	60 mcg per dose
34,000 to 89,999 units/week	17,000 to 44,999 units/week	100 mcg per dose
≥ 90,000 units/week	≥ 45,000 units/week	200 mcg per dose

Administration

For administration using the prefilled syringe, the plunger must be fully depressed during injection to activate the needle guard to activate. Following administration, remove the needle from the injection site and release the plunger to allow the needle guard to move up until the entire needle is covered.

Intravenous (IV):

- **Do not shake as this may denature the glycoprotein rendering the drug biologically inactive.**
- **Do not use if the product has been shaken or frozen.**
- **Avoid prolonged exposure to light, do not mix with any parenteral solution.**
- **Usually administered undiluted.**
- **Administer peripherally or centrally as a bolus injection over <2 minutes; may follow with normal saline flush through the most proximal port; flush volume ≥3 times the line volume.**
- **In patients treated for increasing autologous blood, administer after blood is donated (if applicable).**
- **Do not pool unused portions from the prefilled syringes and do not use the prefilled syringe more than once.**
- **Discard any unused portion.**

Subcutaneous (SC):

- **Administer into the outer upper arm, abdomen (except within 2 inches of the navel), front middle thigh, or the upper outer buttocks area. Rotate injection site; do not inject into areas that are tender, red, bruised, hardened, or scarred or sites with stretch marks.**

General Important Considerations During ESAs Use

1. **ESAs are not a substitute for red blood cell (RBC) transfusion in patients requiring immediate correction of anemia.**
2. **To decrease serious ESAs risks, use the lowest ESA dose sufficient to reduce the need for red blood cell (RBC) transfusions.**
3. **ESA use is less effective in patients with CKD who have absolute or functional iron deficiency, so, it must be combined with iron therapy ((consider iron supplements if serum ferritin is <100 ng/mL or serum transferrin saturation (TSAT) is <20%).**
4. **Before treatment, correct factors impairing erythropoiesis or exclude deficiencies of iron, vitamin B12, and/or folate, as well as other factors that may impair erythropoiesis (inflammatory conditions, infections, bleeding).**
5. **When used for treating anemia due to CKD: initiated when Hb is <10 g/L; however, the decision to initiate therapy must be individualized based on patient-specific factors (e.g., rate of Hb decline, risks of repeat RBC transfusion, symptom severity). The Initial dose will be according to baseline Hb concentration and risk of adverse effects (e.g., cardiovascular).**
6. **Target of Hb in CKD with ESAs use:**

Adult: Target Hb range suggested by KDIGO is 10 to 11.5 g/dL, while manufacturer's labeling recommends a range of 10 to 11 g/dL for patients on dialysis and not exceeding 10 g/dL for patients not on dialysis. Target should be individualized for anticipated benefits and risks.

Pediatric: 12 g/dL (if age ≤16 years), 11 g/dL (if age >16 years) on dialysis & 12 g/dL (if age ≤16 years), 10 g/dL (if age >16 years) for patients not on dialysis.

7. **When the patient achieved target Hb levels on a stable ESA dose and an acute Hb decrease occurs, this is known as loss of efficacy (i.e., acquired hypo-responsiveness). In this case, identify and treat the underlying cause for acute Hb decrease before adjusting the ESA dose and use cautiously the minimum ESA dose to avoid RBC transfusions.**
8. **During dose adjustment: Don't increase the dose more frequently than once every 4 weeks while dose reductions can occur more frequently. Avoid frequent dosage adjustments.**

Monitoring Parameters

Laboratory Monitoring:

Transferrin saturation (TSAT%), serum ferritin (S. ferritin), iron, (before and during treatment) to ensure adequate stores before initiating and throughout therapy; platelet count, electrolytes; Hb/hematocrit (weekly after initiation and following dose adjustments until stable and sufficient to minimize the need for RBC transfusion).

Clinical Monitoring:

BP; monitor for signs of seizures (CKD patients following initiation for first few months, includes new-onset or change in seizure frequency or premonitory symptoms); any cardiovascular or thromboembolic events.

Contraindications

Serious allergic reactions to any ESA products or any component of the formulations; uncontrolled hypertension; pure red cell aplasia (PRCA) that begins after treatment with any ESA products; use in autologous blood donors with MI or stroke in the past month, with unstable angina, or with increased deep venous thrombosis (DVT) risk factors (e.g., history of DVT).

FDA Boxed Warnings for ESAs

Cardiovascular events:

ESAs increase the risk of death, myocardial infarction (MI), stroke, venous thromboembolism, and thrombosis of vascular access when used to target a hemoglobin level of greater than 11g/dl, especially in heart failure.

Chronic Kidney Disease:

No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase the above risks.

Cancer:

ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence as stated in clinical studies.

ESAs are not indicated for patients receiving myelosuppressive chemotherapy when anemia can be managed by transfusion.

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