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Safety of prolonged use of metoclopramide and domperidone as treatment for chronic gastrointestinal dysmotility disorders in patients with systemic sclerosis

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ABSTRACT

Background: Metoclopramide and domperidone are prokinetic agents commonly used to treat gastrointestinal dysmotility disorders. This study aimed to evaluate the safety and associated side effects of prolonged-use metoclopramide and domperidone as treatment for chronic gastrointestinal dysmotility disorders in patients with systemic sclerosis (SSc).

Methods: A quantitative observational survey was conducted by interview questionnaire in rheumatology outpatients at a tertiary teaching hospital in Riyadh, Saudi Arabia. The study included all patients aged 25–80 years diagnosed with SSc. All patients were on metoclopramide or domperidone for the treatment of chronic gastrointestinal dysmotility symptoms over at least 12 weeks.

Results: Eighteen eligible patients were included. Most study participants were diagnosed with SSc complicated by interstitial lung disease (n = 13; 72.2 %). The most frequently reported side effect that occurred while taking prokinetic drugs was shortness of breath (n = 12; 66.7 %). None of the participants reported experiencing depression, galactorrhea, or syncope. CNS side effects were reported in 5.6 %. There were no differences in side effects based on the type and dosage of prokinetic drug used.

Conclusions: Use of metoclopramide and domperidone for the treatment of chronic gastrointestinal dysmotility in SSc patients for 12 weeks or longer was not associated with any troublesome side effects. Further studies with more participants are needed to confirm our findings.

1. Introduction

Systemic sclerosis (SSc) is a rare, sometimes lethal autoimmune disease characterized by progressive fibrosis of connective tissue involving skin, vasculature, and internal organs, including lungs, kidneys, heart, and gastrointestinal (GI) tract (Smith et al., 2018; Volkmann et al., 2023). Etiology of SSc is unknown. Patients with SSc display marked variability in disease manifestations, an observation leading to the categorization of disease subtypes, usually defined by extent of skin involvement (scleroderma) (Pope et al., 2023). Nowadays, most SSc-related mortality is believed due to interstitial lung disease (ILD) or pulmonary arterial hypertension (PAH) (Bukiri & Volkmann, 2022). However, the burden of GI morbidity is considerable and affects nearly all (>90 %) patients, often resulting in GI obstruction, gastroesophageal reflux, nausea, vomiting, diarrhea, and malnutrition (Frech & Mar, 2018; Pope et al., 2023).

With the possible exception of autologous hematopoietic stem cell transplantation (AHSCT), which due to its high risk of treatment-related toxicity is reserved only for advanced cases with poor prognosis, there are no proven disease-modifying drugs for SSc. Rather, a recommended approach to treatment entails screening assessment to identify active organ involvement and provision of therapies targeted against organ-specific complications of the disease (Bukiri & Volkmann, 2022). In patients with SSc causative of GI dysmotility, that is, disrupted enteric

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neuromuscular coordination (Ladopoulos et al., 2018; Twist et al., 2018), prokinetic drugs may be useful to stimulate and enhance normalized GI motility (Acosta & Camilleri, 2015). Of these agents, the dopamine receptor antagonists metoclopramide and domperidone may be effective for the management of motor disorders of the GI tract through blockade of enteric (neuronal and muscular) inhibitory D_2 receptors and $5HT_4$ agonistic effects (Tonini et al., 2004). It is believed the major prokinetic effect of these agents is antagonism of dopamine-mediated relaxation of GI smooth muscle. These pharmacologic actions may lead to improved GI peristalsis and increased gastric emptying.

Despite their effectiveness both metoclopramide and domperidone may be associated with serious side effects including, respectively, extrapyramidal symptoms, hyperprolactinemia, and (rarely) neuroleptic malignant syndrome (Moos & Hansen, 2008) and headache, drowsiness, dizziness, diarrhea (Hale et al., 2018), and cardiac abnormalities such as tachycardia, palpitations, and QT prolongation (Bashashati et al., 2016). Therefore for both drugs it is recommended to use the lowest effective dose for the shortest duration necessary to control symptoms.

This study aimed to evaluate the safety of prolonged use (>12 weeks) of metoclopramide oral tablet 10, 20, or 30 mg/day and domperidone oral tablet 10, 20, or 30 mg/day for the treatment of chronic GI dysmotility disorders in patients with SSc.

2. Methods

2.1. Study design and settings

A quantitative observational survey using patient interviews was conducted to investigate the safety of treatment with prokinetic agents, domperidone and metoclopramide. Interviewed were Saudi patients with chronic GI dysmotility related to SSc receiving treatment at specialized rheumatology clinics at a tertiary teaching hospital in Riyadh, Saudi Arabia.

2.2. Ethics

The Institutional Review Board (IRB) Approval Number: E-19–3848 was obtained before initiating this study. A written consent form was obtained from all participants, indicating the study's purpose and the right to withdraw at any time. Patients were assigned code numbers to preserve their anonymity. No incentives or rewards were given.

2.3. Eligibility criteria

Included were 25–80-year-old male and female SSc patients presenting with GI dysmotility defined as gastroparesis based on typical symptoms and/or gastroesophageal reflux disease (GERD). Patients had to have received either metoclopramide or domperidone for the amelioration of symptoms consistent with chronic GI dysmotility for at least 12 weeks. Only patients who took at least one daily dose of study drug were deemed compliant and enrolled; non-compliance was an exclusion criterion.

2.4. Participant enrollment

Patients were recruited during follow-up visits to the outpatient clinics. During clinic times, the study's team visited the specialized rheumatology outpatient clinics and interviewed all patients who met the inclusion criteria. All study participants provided written informed consent before conducting the interview, and their confidentiality was strictly protected. Clinical pharmacists were assigned to collect the data by following a uniform process. The study data were collected through face-to-face interviews conducted between March and June 2019.

2.5. Study instrument

The study's dataset was collected using an interview-based questionnaire. The questionnaire was developed based on an extensive literature review of reported side effects and experts' opinions to meet the study objectives (Camilleri, 2007; Schey et al., 2016). The questionnaire was designed to interrogate patients' demographics (sex, age, nationality, and highest education level) as well as relevant medical history, medication history, and experienced side effects.

Since no prior validated questionnaire was available for the study question, a literature review was performed to elucidate reported side effects of the study medications. The data were reviewed by two authors who are experts in the field. The survey questions were then generated for the purpose of patient interviews. A preliminary investigation of the queationnaire's usefulness was performed by administering the questionnaire in a small sample of patients. The results of this preliminary investigation and any issues encountered were reviewed by the two experts, and the survey tool was modified accordingly. Hence the questionnaire's reliability was internally validated by test–retest method. The study questionnaire was initially developed in English and translated into Arabic using reliable methodology (WHO, 2017).

2.6. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23.0 software (IBM, Chicago, IL). Karl Pearson's coefficient of correlation was used to assess the reliability of the study tool using the parallel forms method. Descriptive statistical methods were used to calculate frequencies and percentages of all nominal variables. Inferential statistical tests, including the Chi-square test or Fisher's exact test, were used to correlate reported safety data with prokinetic drug use. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Participants' socio-demographic and clinical characteristics

A total of 23 participants were enrolled, of whom 18 (M/F n = 4/14) fulfilled the inclusion criteria. Most participants were aged over 65 years (n = 7; 38.9 %), and most (77.8 %) had a good educational level, with at least a high school diploma (Table 1).

3.2. Clinical status

Most 72.2 % participants had SSc complicated by ILD. Domperidone

Table 1
Distribution of socio-demographic characteristics of study subjects (n = 18).

Participants' characteristics	n (%)
Age group	
26–39 years	4 (22.2 %)
40–54 years	4 (22.2 %)
55–64 years	3 (16.7 %)
≥65 years	7 (38.9 %)
Sex	
Male	4 (22.2 %)
Female	14 (77.8 %)
Nationality	
Saudi	16 (88.9 %)
Non-Saudi	2 (11.1 %)
Education level	
Lower than high school	4 (22.2 %)
High school diploma or GED	7 (38.9 %)
College degree or higher	6 (33.3 %)
Other	1 (5.6 %)

was used in 77.8 % and metoclopramide in 22.2 % (Table 2). Other drugs concomitantly used by participants included mycophenolate mofetil (MMF) in three patients, sildenafil in four patients, and rituximab in two patients. These medications were prescribed for the alleviation of SSc and/or ILD symptoms; patients had been receiving them long-term prior to study commencement and no dosing interruptions were observed during the study period.

3.3. Reported side effects of prokinetic agents

For the two prokinetic agents analyzed shortness of breath was the most frequently reported side effect (66.7 %). Chest pain, palpitations, and increased appetite were each reported by 22.2 %. Neurologic side effects (including tremors, somnolence, and extrapyramidal symptoms) were reported in 5.6 %. Depression, galactorrhea, and syncope were not reported by any of the study participants. No other side effects were reported (Table 3).

3.4. Side effects according to prokinetic agent

Side effects reported specifically for domperidone and metoclopramide are displayed in Table 4. There were no statistically significant differences between these two groups in developing any side effects. Palpitations, shortness of breath, vomiting, and increased appetite were reported by participants using either agent. Side effects reported by domperidone users only were headache (14.3 %), tremors, anxiety, somnolence, extrapyramidal symptoms (all 7.1 %), chest pain (28.6 %), and dizziness (21.4 %). The most frequently reported side effect for both groups was shortness of breath.

3.5. Side effects according to dosage

No statistically significant difference of side effects profiles was noted in patients stratified according to their daily dosing frequency

Table 2
Diagnoses distribution and prokinetics use.

Participants' responses	n (%)
Are you diagnosed with SSc or SSc / ILD?	
SSc	5 (27.8 %)
SSc complicated by ILD	13 (72.2 %)
Based on your symptoms, has your physician treated you for chronic GI dysmotility?	
Yes	18 (100 %)
No	0 (0.0 %)
Have you ever used prokinetic agents (metoclopramide / domperidone)?	
Yes	18 (100 %)
No	0 (0.0 %)
How long have you used prokinetic agents (metoclopramide / domperidone)?	
More than 12 weeks	18 (100 %)
Less than 12 weeks	0 (0.0 %)
Were you using prokinetic agent daily?	
Yes	18 (100 %)
No	0 (0.0 %)
If yes, how many times / day do you use prokinetic agent?	
Once	4 (22.2 %)
Twice	10 (55.6 %)
Three or more times	4 (22.2 %)
Which prokinetic agent did you use?	
Metoclopramide	4 (22.2 %)
Domperidone	14 (77.8 %)

SSc, systemic sclerosis; ILD, interstitial lung disease.

Table 3
Participant-reported side effects of prokinetic agents (n = 18).

Side effect	n (%)
Headache	2 (11.1 %)
Tremors	1 (5.6 %)
Anxiety	1 (5.6 %)
Somnolence	1 (5.6 %)
Depression	0 (0.0 %)
Extrapyramidal effects	1 (5.6 %)
Galactorrhea/breast tenderness	0 (0.0 %)
Palpitations	4 (22.2 %)
Chest pain	4 (22.2 %)
Dizziness	3 (16.7 %)
Syncope	0 (0.0 %)
Shortness of breath	12 (66.7 %)
Vomiting	3 (16.7 %)
Increased appetite	4 (22.2 %)
Others	0 (0.0 %)

Table 4
Side effects associated with specific prokinetic agent.

	Which prokinetic agent did you use?		p-value
	Metoclopramide (n = 4)	Domperidone (n = 14)	
	n (%)	n (%)	
Headache	0 (0.0 %)	2 (14.3 %)	0.595
Tremors	0 (0.0 %)	1 (7.1 %)	0.778
Anxiety	0 (0.0 %)	1 (7.1 %)	0.778
Somnolence	0 (0.0 %)	1 (7.1 %)	0.778
Depression	0 (0.0 %)	0 (0.0 %)	—
Extrapyramidal effects	0 (0.0 %)	1 (7.1 %)	0.778
Galactorrhea/ breast tenderness	0 (0.0 %)	0 (0.0 %)	—
Palpitations	2 (50.0 %)	2 (14.3 %)	0.197
Chest pain	0 (0.0 %)	4 (28.6 %)	0.327
Dizziness	0 (0.0 %)	3 (21.4 %)	0.446
Syncope	0 (0.0 %)	0 (0.0 %)	—
Shortness of breath	2 (50.0 %)	10 (71.4 %)	0.407
Vomiting	2 (50.0 %)	1 (7.1 %)	0.108
Increased appetite	2 (50.0 %)	2 (14.3 %)	0.197
Others	0 (0.0 %)	0 (0.0 %)	—

Table 5
Side effects per prokinetic agent dosing frequency.

	How many times / day did you use prokinetic agent?			p-value
	Once (n = 4)	Twice (n = 10)	Thrice (n = 4)	
	n (%)	n (%)	n (%)	
Headache	0 (0.0 %)	1 (10.0 %)	1 (25.0 %)	0.524
Tremors	1 (25.0 %)	0 (0.0 %)	0 (0.0 %)	0.157
Anxiety	1 (25.0 %)	0 (0.0 %)	0 (0.0 %)	0.157
Somnolence	1 (25.0 %)	0 (0.0 %)	0 (0.0 %)	0.157
Depression	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	—
Extrapyramidal effects	1 (25.0 %)	0 (0.0 %)	0 (0.0 %)	0.157
Galactorrhea/breast tenderness	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	—
Palpitations	0 (0.0 %)	3 (30.0 %)	1 (25.0 %)	0.470
Chest pain	2 (50.0 %)	1 (10.0 %)	1 (25.0 %)	0.263
Dizziness	1 (25.0 %)	1 (10.0 %)	1 (25.0 %)	0.698
Syncope	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	—
Shortness of breath	3 (75.0 %)	5 (50.0 %)	4 (100 %)	0.185
Vomiting	1 (25.0 %)	2 (20.0 %)	0 (0.0 %)	0.583
Increased appetite	2 (50.0 %)	2 (20.0 %)	0 (0.0 %)	0.228
Others	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	—

(once, twice, or thrice daily; Table 5).

4. Discussion

This study evaluated the safety of prolonged use of the prokinetic agents metoclopramide and domperidone in patients diagnosed with SSc or SSc complicated by ILD who experienced symptoms suggestive of chronic GI dysmotility requiring treatment. Domperidone and metoclopramide were the prokinetic agents evaluated because they are commonly prescribed by healthcare providers in Saudi Arabia (Brown & Khanderia, 1990).

Both metoclopramide and domperidone are known to exert a number of unwanted side effects including CNS and cardiovascular side effects (Brogden et al., 1982; Isola et al., 2023). In the present study patients who used domperidone reported numerically albeit nonsignificantly higher rates of side effects than those who used metoclopramide. Side effects including palpitations, shortness of breath, vomiting, and increased appetite were associated with both agents.

Domperidone minimally crosses the blood–brain barrier and is rarely associated with CNS side effects (Reddymasu et al., 2007). A double-blind, multicenter study that compared domperidone versus metoclopramide for diabetic gastroparesis reported CNS side effects are more pronounced with metoclopramide (Patterson et al., 1999). On the other hand, metoclopramide may cause drug-induced movement disorders or exacerbate various extrapyramidal disorders (Miller & Jankovic, 1989). Metoclopramide is FDA approved and the most widely used agent to treat GI dysmotility; it is listed as an essential drug on the World Health Organization (WHO) List of Essential Medicines (Pasricha et al., 2006; Shakhatrehet al., 2019; WHO, 2021). Yet, metoclopramide could produce serious CNS side effects (Donnet et al., 1991). Metoclopramide has been indicated as the second most common agent after Haldol responsible for 39.4 % of cases with tardive dyskinesia (Kenney et al., 2008). However, none of our participants who used metoclopramide (n = 4) reported CNS side effects despite prolonged use (>12 weeks). Because of the small sample size, this cannot be generalized.

Domperidone's rare yet most serious known side effect is sudden cardiac death. This seems especially hazardous for domperidone given at higher dosages > 30 mg/day (van Noord et al., 2010). A case-control study concluded that high-dose domperidone users (40–120 mg/day) were at increased risk of developing serious ventricular arrhythmia and sudden cardiac death (Johannes et al., 2010). Our participants who used low-dose domperidone (10–30 mg/day) had no baseline ECG prior to commencing treatment. Cardiovascular complaints reported by our participants included palpitation, chest pain, and shortness of breath, which were not significantly different between treatment groups. Indeed, these complaints may have been due to underlying systemic disease, especially since most of the study participants were diagnosed with SSc complicated by ILD.

Domperidone and metoclopramide have been reported to cause hyperprolactinemia, which may produce symptoms of galactorrhea, menstrual disturbance, and impotence (Molitch, 2005). None of our participants (on domperidone or metoclopramide) manifested any hyperprolactinemia-related side effects.

The main strength of this study is it is the first investigation of side effects associated with prolonged use (>12 weeks) of commonly used prokinetic agents for the treatment of GI dysmotility in patients with SSc in Saudi Arabia. However, limitations include the dataset was collected using a rather limited number of participants. The inclusion criterion of prolonged use of prokinetic agents placed a strong constraint on expanding the study population.

5. Conclusion

This study suggests domperidone and metoclopramide given at low daily dosages in SSc patients for the management of SSc-related GI dysmotility are not associated with marked safety concerns. Further studies with more participants and different experimental designs are needed to evaluate the safety of prolonged prokinetic agent use in this setting.

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Conflict of Interest: The authors declare no conflicts of interest.

Ethical approval: King Saud University, College of Medicine Institutional Review Board (IRB) approval (E-19–3848) was obtained to conduct this study.

CRediT authorship contribution statement

Saad Alkhowaiter: Conceptualization, Methodology, Data curation, Writing – original draft. **Maha M. Al Rasheed:** Conceptualization, Methodology, Data curation. **Nuha Alammar:** Conceptualization, Methodology, Data curation. **Ammar Alotaibi:** Conceptualization, Methodology, Data curation. **Mansour Altuwaijri:** Conceptualization, Methodology, Data curation. **Suliman Alshankiti:** Conceptualization, Methodology, Data curation. **Mohammed A. Omair:** Conceptualization, Methodology, Data curation. **Majid Alsahafi:** Conceptualization, Methodology, Data curation.

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References

Acosta, A., Camilleri, M., 2015. Prokinetics in gastroparesis. Gastroenterol. Clin. North Am. 44, 97–111.
Bashashati, M., Sarosiek, I., Siddiqui, T., McCallum, R.W., 2016. Adverse effects of domperidone: prolonged QuesT for knowledge? Dig. Dis. Sci. 61, 3384–3386.
Brogden, R.N., Carmine, A.A., Heel, R.C., Speight, T.M., Avery, G.S., 1982. Domperidone. a review of its pharmacological activity, pharmacokinetics and therapeutic efficacy in the symptomatic treatment of chronic dyspepsia and as an antiemetic. Drugs 24, 360–400.
Brown, C.K., Khanderia, U., 1990. Use of metoclopramide, domperidone, and cisapride in the management of diabetic gastroparesis. Clin. Pharm. 9, 357–365.
Bukiri, H., Volkmann, E.R., 2022. Current advances in the treatment of systemic sclerosis. Curr. Opin. Pharmacol. 64, 102211.
Camilleri, M., 2007. Clinical practice. Diabetic Gastroparesis. N. Engl. J. Med. 356, 820–829.
Donnet, A., Harle, J.R., Dumont, J.C., Cherif, A.A., 1991. Neuroleptic malignant syndrome induced by metoclopramide. Biomed. Pharmacother. 45, 461–462.
Frech, T.M., Mar, D., 2018. Gastrointestinal and hepatic disease in systemic sclerosis. Rheum. Dis. Clin. North Am. 44, 15–28.
Hale, T.W., Kendall-Tackett, K., Cong, Z., 2018. Domperidone versus metoclopramide. Clin. Lact. 9, 10–18.
Isola, S., Hussain, A., Dua, A., Singh, K., Adams, N., 2023. Metoclopramide. StatPearls.
Johannes, C.B., Varas-Lorenzo, C., McQuay, L.J., Midkiff, K.D., Fife, D., 2010. Risk of serious ventricular arrhythmia and sudden cardiac death in a cohort of users of domperidone: a nested case-control study. Pharmacoepidemiol. Drug Saf. 19, 881–888.
Kenney, C., Hunter, C., Davidson, A., Jankovic, J., 2008. Metoclopramide, an increasingly recognized cause of tardive dyskinesia. J. Clin. Pharmacol. 48, 379–385.
Ladopoulos, T., Giannaki, M., Alexopoulou, C., Proklou, A., Pediaditis, E., Kondili, E., 2018. Gastrointestinal dysmotility in critically ill patients. Ann. Gastroenterol. 31, 273–281.
Miller, L.G., Jankovic, J., 1989. Metoclopramide-induced movement disorders: clinical findings with a review of the literature. Arch. Intern. Med. 149, 2486–2492.
Molitch, M.E., 2005. Medication-induced hyperprolactinemia. Mayo Clin. Proc. 80, 1050–1057.
Moos, D.D., Hansen, D.J., 2008. Metoclopramide and extrapyramidal symptoms: a case report. J. Perianesth. Nurs. 23, 292–299.
Pasricha, P.J., Pehlivanov, N., Sugumar, A., Jankovic, J., 2006. Drug insight: from disturbed motility to disordered movement—a review of the clinical benefits and medicolegal risks of metoclopramide. Nat. Clin. Pract. Gastroenterol. Hepatol. 3, 138–148.
Patterson, D., Abell, T., Rothstein, R., Koch, K., Barnett, J., 1999. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. Am. J. Gastroenterol. 94, 1230–1234.
Pope, J.E., Denton, C.P., Johnson, S.R., Fernandez-Codina, A., Hudson, M., Nevskaya, T., 2023. State-of-the-art evidence in the treatment of systemic sclerosis. Nat. Rev. Rheumatol. 19, 212–226.

Reddymasu, S.C., Soykan, I., McCallum, R.W., 2007. Domperidone: review of pharmacology and clinical applications in gastroenterology. Am. J. Gastroenterol. 102, 2036–2045.
Schey, R., Saadi, M., Midani, D., Roberts, A.C., Parupalli, R., Parkman, H.P., 2016. Domperidone to treat symptoms of gastroparesis: benefits and side effects from a large single-center cohort. Dig. Dis. Sci. 61, 3545–3551.
Shakhatreh, M., Jehangir, A., Malik, Z., Parkman, H.P., 2019. Metoclopramide for the treatment of diabetic gastroparesis. Expert Rev. Gastroenterol. Hepatol. 13, 711–721.
Smith, V., Scirè, C.A., Talarico, R., Airo, P., Alexander, T., Allanore, Y., 2018. Systemic sclerosis: state of the art on clinical practice guidelines. RMD Open 4 (Suppl 1), e000782.
Tonini, M., Cipollina, L., Poluzzi, E., Crema, F., Corazza, G.R., De Ponti, F., 2004. Review article: clinical implications of enteric and central D_2 receptor blockade by antidopaminergic gastrointestinal prokinetics. Aliment. Pharmacol. Ther. 19, 379–390.
Twist, K., Ablett, J., Wearden, A., Paine, P., Vasant, D., Lal, S., Peters, S., 2018. Gastrointestinal dysmotility: a qualitative exploration of the journey from symptom onset to diagnosis. Neurogastroenterol. Motil. 30, e13339.
van Noord, C., Dieleman, J.P., van Herpen, G., Verhamme, K., Sturkenboom, M.C.J.M., 2010. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. Drug Saf. 33, 1003–1014.
Volkmann, E.R., Andréasson, K., Smith, V., 2023. Systemic sclerosis. Lancet 401, 304–318.
Who, 2017. Management of substance abuse: process of translation and adaptation of instruments. Accessed May 2023. http://www.who.int/substance_abuse/research_tools/translation/en/.
WHO model list of essential medicines: 22nd list (2021). World Health Organization. https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02 (accessed May 2023).