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GLOBAL WARMING AND PRESCRIBING: A REVIEW ON MEDICINES' EFFECTS AND PRECAUTIONS

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ABSTRACT

Introduction: *Global warming is slowly but surely becoming one of the greatest problems of the modern world. Heatwaves with extremely high temperatures and humidity changes are particularly dangerous as they can lead to increased mortality rates and increased side effects of certain medications.*
The goal of this study was to give a short review of the most critical issues healthcare professionals should be mindful of when it comes to prescription of medicines during high temperature periods.

Methods: *A PubMed literature search was conducted in January 2021 in order to identify studies showing stability changes of most prescribed drugs in high temperatures as well as studies demonstrating impact of some drugs on human thermoregulation.*

Results: *A vast majority of the commonly prescribed drugs, including Simvastatin, Levothyroxine, Omeprazole and Atorvastatin aren't susceptible to heat. However, some studies found that Amlodipine and Lansoprazole degrade following heat exposure. A study demonstrated the effects of low relative humidity environment on Levothyroxine tablets. While Levothyroxine remained stable at high temperatures, it significantly degraded with the decrease in humidity. Since all vaccines, both viral and bacterial, are most stable at exactly 2-8 C, providing adequate storage has turned out to be an immense challenge. In general, killed whole-cell bacterial vaccines, like pertussis vaccine, show a higher degree of stability of potency compared to live attenuated vaccines, such as BCG. However, when tested in high-temperature conditions, BCG vaccine has proven to be more stable than Pertussis vaccine. Also, diphtheria and tetanus toxoids have proven to be most stable during exposure to various conditions. Many medicines can potentially have their side effects enhanced during heatwaves and cause serious health issues. Using the percutaneous form of nitroglycerin could lead to an additional decrease in blood pressure in warm weather. Subdermally injected insulin could create a severe hypoglycemia in diabetic patients. Studies have shown that schizophrenic patients on antipsychotic treatment have much lower heat tolerance, with a higher possibility of developing hyperthermic syndromes such as febrile catatonia or neuroleptic malignant syndrome.*

Conclusion: *Heatwave periods are not to be taken lightly and should be approached with utmost caution when prescribing therapy. It is of critical importance to inform and educate vulnerable populations early in the season and promote proper hydration throughout the periods when temperatures exceed local averages.*

Keywords: *global warming, heatwave, medicine stability, vaccine*

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INTRODUCTION

Global warming is gradually changing the world as we know it. The environmental temperature increase is only one of its many consequences, and numerous studies have already shown a significant increase in mortality during heatwaves (Guo et al. 2018; Pham et al. 2019). Heatwave, by definition, includes three or more consecutive days during which the air temperature is above 32,2C (Bouchama & Knochel 2002). Alongside extreme temperatures, humidity changes remain the most critical factor, even though their importance is often understated. The most common cause of death during periods of increased environmental temperature is heat stroke, a life-threatening illness characterized by a core body

temperature above 40°C and central nervous system abnormalities (Bouchama & Knochel 2002). Consequently, it is tremendously important, particularly for medical professionals, to be acquainted with medicines that are challenging for usage during heatwaves (Westaway et al. 2015). Particular caution should be given to storage (Woodrow 2009), as well as prescribing of certain medications during hot weather. Unfortunately, there are very few studies regarding this problem in the scientific literature. Our aim here was to give a short review of the most critical issues healthcare professionals should be mindful of when it comes to prescribing of medicines in times of high temperatures.

SUBJECTS AND METHODS

In January 2021, we conducted a Pub Med search by using the following key words "prescribing", "heatwave", "stability", "high temperatures", "heat", "heat stroke", "drugs", and "medicine" in order to identify published articles of interest for this review. All identified studies were read by the co-authors and all articles dealing with effects of medicines during elevated environmental temperatures were included. All animal studies were excluded from further analysis, except for the one describing central angiotensin receptor blockade in rats which could have significant value for further human studies. The NSH database was used to find the most prescribed and the most expensive UK medicines. Results were grouped in order to compare and analyse the most commonly prescribed and the most expensive UK medicines, vaccines and medicines which most interfere with thermoregulation.

STABILITY OF CERTAIN MEDICINES CHANGES IN HIGH TEMPERATURES

A vast majority of the most prescribed drugs, including Simvastatin, Levothyroxine, Omeprazole and Atorvastatin aren't susceptible to degradation due to dry heat (Knapik-Kowalczuk et al. 2019; Oliveira et al. 2013; Shah et al. 2019). Simvastatin showed no decomposition when heated at 100 and 150°C, although it was observed under reduced pressure (13.3 Pa) (Simões et al. 2014). In a study, preparations of Levothyroxine in the dry powder form, or dispersed in water-like or oil-like solvents, were heated at temperatures ranging from 65 to 160°C for 5 to 15 min periods. Heating Levothyroxine to 72°C produced less than 10% degradation. Thermal degradation was significant only above 90°C, a temperature which hopefully won't be reached during heatwave periods (Wortsman J et al. 1989). However, Amlodipine and Lansoprazole both showed some degradation because of heat exposure (Shah et al. 2008). Lansoprazole is an extreme example of this, degrading 10% in the first 8 hours of exposure at room temperature (Polonini et al. 2018). A dry heat degradation study of Atorvastatin (10 µg/ml) and Amlodipine (10 µg/ml) at 80°C for 2h showed two degradation product peaks at 3.06 and 3.37 min for Amlodipine, while Atorvastatin remained stable (Shah et al. 2008). (Figure 1.) However, humidity also plays a significant role in the overall stability of certain stored drugs (Podczeck et al. 1997). Therefore, a low relative humidity (RH) environment

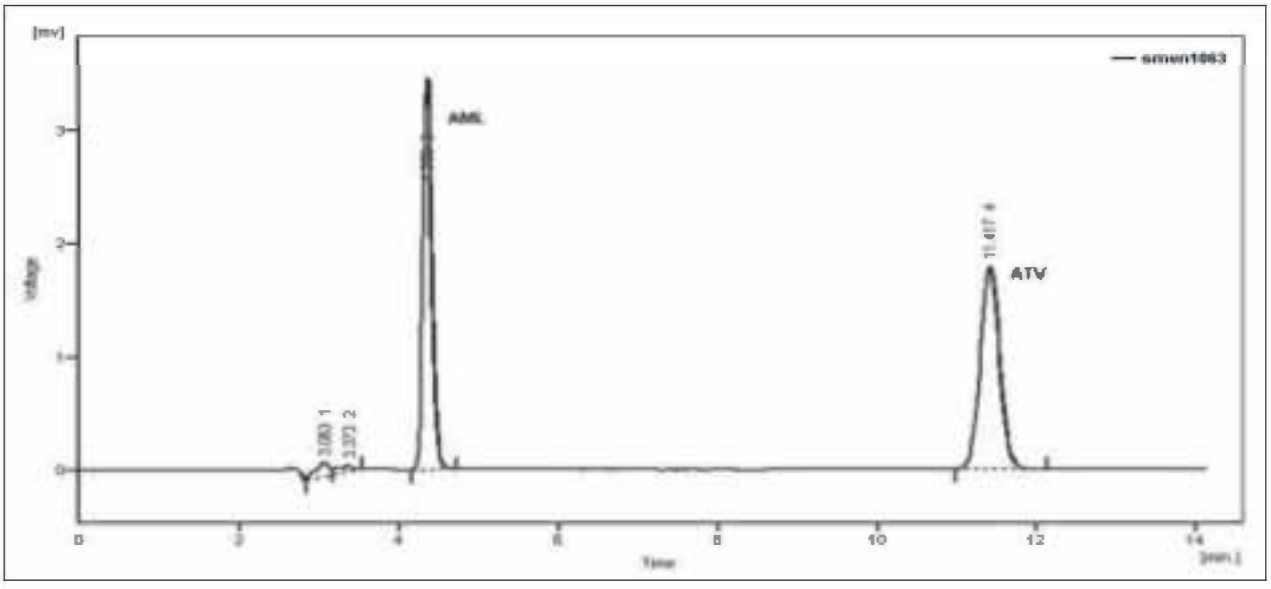

Figure 1.
Chromatogram of dry heat degradation study of Atorvastatin (ATV) 10 µg/ml and Amlodipine (10 µg/ml) at 80°C for 2 h (Shah et al. 2008).

can cause accelerated degradation. Levothyroxine tablets are the most recalled drug product in the history of USFDA (United States Food and Drug Administration). A study (Wortsman J et al. 1989) demonstrated that the amount of Levothyroxine in the samples stored at room temperature (RT)/75% RH and 60 °C/75% RH remained relatively constant. In contrast, the amount of Levothyroxine for samples stored at RT/4–6% RH and 60 °C/4–6% RH decreased rapidly. At the end of 32 days, the amount of Levothyroxine remaining in the sample stored at RT/4–6% RH decreased by 23.75% and at 60 °C/4–6% RH decreased by 33.1% (Wortsman J et al. 1989). This is just an example of a drug that is stable at high temperatures but becomes very fragile if humidity change is added into the equation. Many more drugs could follow the same pattern. Unfortunately, studies that include multiple humidity levels for their drug stability testing are very rare. Similar problems exist with biological medicines and elevated environmental temperatures, especially since biologicals predominantly fall into the category of the most expensive drugs on the market. It is uncertain whether Adalimumab, which is at the very top of the list of medicines by the total estimated cost at list price for medicines positively appraised by NICE (National Health Service 2018), could remain stable at temperatures higher than its approved storage conditions of 25 C (up to 14 days) (Park et al. 2019). Etanercept has been demonstrated to be stable for up to 1 month at 25 C (Shannon et al. 2017). Ranibizumab and Aflibercept both demonstrated satisfactory stabilityeven when incubated at 37 C up to 30 days (Moreno et al. 2016). On the other hand, more concerning facts are that recent studies have showed uncertainty about the anticoagulant effect of dabigatran and rivaroxaban at higher environmental temperatures (Stöllberger & Finsterer 2013), making their safety and efficacy when used during heatwaves questionable.

VACCINES

It is also worth mentioning that vaccines are among the most fragile medicines temperature-wise, but at the same time, one of the most successful cost-effective interventions throughout the history of medicine (Kartoglu & Milstien 2014). For decades, scientists have been trying to develop strategies and establish a cold supply chain that would make vaccines available to all parts of the world, regardless of life quality and climate conditions. A 2012 American study showed that in 76% of the providers of the children vaccine, the products were exposed to inappropriate temperatures for at least five consecutive hours during a 2-week trial

Table 1. Top 10 medicines by total estimated cost at list price for medicines positively appraised by NICE, prescribed or issued in all sectors, 2017/18 (National Health Service 2018)

Medicine	Condition	Total cost (£000s)
adalimumab	Moderate to severe hidradenitis suppurativa	494.495,8
Aflibercept (solution for injection)	Visual impairment caused by macular oedema after branch retinal vein occlusion	365.578,8
etanercept	TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis	219.849,8
infliximab	Rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed	200.696,5
rivaroxaban	Preventing adverse outcomes after acute management of acute coronary syndrome	183.209,1
apixaban	Treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism	182.293,6
trastuzumab	HER2-positive breast cancer	163.761,9
ranibizumab	Choroidal neovascularisation associated with pathological myopia	153.837,1
rituximab	Anti-neutrophil cytoplasmic antibody-associated vasculitis	153.520,7
lenalidomide	Myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality	146.804,7

period. This kind of storage conditions could reduce vaccines' efficacy, leading to a higher risk of failing to provide the children with the maximum protection possible (Levinson 2012). Since all vaccines, both viral and bacterial, are most stable at exactly 2-8 C (Table 2.), providing adequate storage has turned out to be an immense challenge (Corbel 1996; Jeremijenko et al. 1996; Thakker & Woods 1992), which requires detailed knowledge about types and characteristics of each product. Even in the same group of vaccines, taking bacterial vaccines as an example, there is a wide range of variations stability-wise. It is very interesting that in general, killed whole-cell bacterial vaccines, like pertussis vaccine, show a higher degree of stability of potency compared to live attenuated vaccines, such as BCG (Corbel 1996). However, tested in high-temperature conditions, BCG vaccine has proven to be more stable than Pertussis vaccine (Table 2.) (World Health Organization 2006). Also, diphtheria and tetanus toxoids have proven to be most stable in exposure to various conditions (Corbel 1996; World Health Organization 2006). It is not just heat that is dangerous for the stability of the vaccines but also freezing of the product itself. Sometimes, in the cold chain process, storage temperatures can be decreased below 2 C. This can lead to a decline of potency in some vaccines, like inactivated poliovirus vaccine, which is completely unstable after freezing. On the other hand, some vaccines, such as oral poliovirus vaccine are even better preserved frozen and require storage at -20 C (White et al. 2018). Taking these two at first sight similar vaccines as an example, it is striking how easy it is to affect the stability of a product if one has a lack of knowledge about appropriate storing conditions. Moreover, even the slightest temperature alteration in the environment can lead to a change of storage temperature (Vangroenweghe 2017), which could mean great product losses – with both financial and medical consequences (Bell et al. 2001). According to 2009/10 data, England spends 0,4% of its healthcare budget on vaccines, which would come around at 10 EUR per capita (Ethgen et al. 2016). Reflecting on the fact that total health spending in England in 2018/19 was 129 billion GBP (Full Fact Team 2019), more than 500 million GBP is spent on vaccines each year. Unfortunately, there was no available data on the percentage of vaccines being damaged due to extreme environmental conditions. Still, the significance of the prospective losses can be perceived from the previously stated data. In the past few decades, there have been considerable improvements in this area. Some vaccines which were very susceptible to temperature variations, such as oral poliovirus vaccine (Arya 1988), have been modified to become more stable (Bark 1998). Furthermore, more attention has been awarded to the importance of preventing vaccine freezing as well as tailoring cold chains to make them better at addressing particular needs of specific situations (Kartoglu & Milstien 2014). However, considering the undeniable climate changes and temperature increase, there is still a lot of room for improvement to prevent a step back in immunization and eradication of some of the deadliest infectious diseases. This problem is especially relevant to the developing countries, who are facing a new challenge in the vaccine supply and logistics system (Zaffran et al. 2013), having in mind that they will be the ones who will be the most affected by the temperature increase as a consequence of the global warming (King & Harrington 2018). Education of medical professionals and organizations in charge of vaccine storage and transport is the critical step in the whole cold chain process.

DISCUSSION

SOME MEDICINES INTERFERE WITH THERMOREGULATION LEADING TO HIGHER RISK OF HEATSTROKE

During extreme weather conditions, thermoregulation plays a crucial role in maintaining physiologic body temperature. Researchers have shown that heat strokes result from thermoregulatory failure coupled with an exaggerated acute-phase response and possibly with altered expression of heat-shock proteins (Bouchama & Knochel 2002). Also, it is worth mentioning that at higher temperatures, saturation specific humidity increases, and relative humidity decreases. Saturation specific humidity is the maximum amount of water vapor that air can contain without precipitating out. At sea level and temperatures above freezing, the saturation specific humidity increases by approximately 6% per degree Celsius (Wehner et al. 2017). Relative humidity (RH) is the amount of moisture in the air compared to what the air can "hold" at that temperature. Humans can be comfortable within a wide range of humidities depending on the weather, from 30% to 70%, but ideally between 50% and 60%. Humidity also plays a significant role in body cooling, especially in areas of the world that are already moister than others. The rate of evaporative cooling is controlled by the difference between the actual specific humidity, the amount of water vapor in the air, and the saturation specific humidity (Wehner et al. 2017). In order for the relative humidity to reach 100% and render sweating ineffective as a cooling mechanism, the actual humidity has to be the same value as the saturation specific humidity. Therefore, those already humid areas become even more humid at higher temperatures as the air can hold much more water vapor. Many medicines can potentially have their side effects enhanced during heatwaves and cause serious health issues. Environmental heat can affect the bioavailability and pharmacokinetics of some drugs. The degree of drugs absorption administered transdermally and subcutaneously is increased with higher temperatures and humidity. This seems to be predominantly related to

Table 2. Stability of vaccines commonly used in national immunization programmes (World Health Organization 2006)

Type	Vaccine	Storage temperature, °C				
		2-8	20-25	37	>45	Freezing
Viral vaccines	Oral poliovirus vaccine	Stable for up to 1 year	Stable for weeks	Stable for 2 days	Unstable	Stable
	Inactivated poliovirus vaccine	Stable for 1-4 years	Stable for weeks	Stable for weeks	Little data available	Unstable
	Hepatitis B vaccine	Stable for >4 years	Stable for months	Stable for weeks	At 45C, stable for days	Unstable
	Measles, mumps, rubella vaccines	Stable for 2 years	Stable for at least one month	Stable for at least one week	Unstable	Stable
	Yellow fever	Stable for >2 years	Stable for months	Stable for two weeks	Unstable	Stable
Bacterial vaccines	Pertussis vaccine	Stable for 18-24 months	Stable for 2 weeks	Stable for one week	10% or more loss of potency per day	Unstable
	BCG vaccine	Stable for 1-2 years	Stable for months	Loss of no more than 20% after one month	Unstable	Stable
	Tetanus and diphtheria toxoids, monovalent or components of combined vaccines	Stable for >3 years	Stable for months	Stable for months	Unstable above 55C	Unstable

heat-induced local vasodilatation and accelerated skin blood flow (Klemsdal et al. 1992; Smirnova et al. 2019). A study (Klemsdal et al. 1992) demonstrated a correlation between blood flow and transdermal absorption of nitroglycerin by locally heating nitroglycerin patches placed on multiple areas of the upper arm. Results after heating for 15 minutes were enhanced local blood perfusion and simultaneously significantly increased nitroglycerin plasma concentrations. Therefore, using the percutaneous form of nitroglycerin could lead to an additional decrease in blood pressure during warm weather. Taking injected insulin subdermally could create a severe hypoglycemia in diabetic patients (Smirnova et al. 2019). The elimination of drugs with high hepatic extraction rates is affected by changes in hepatic blood flow (Brockmöller & Ivar 1994). Increased skin blood flow can, as a result, have decreased blood flow to the internal organs and therefore reduced hepatic clearance of drugs. That is much more likely to occur during prolonged heat exposure (1-3 hours) as opposed to short term exposure (Vanakoski & Seppälä 1998). The indocyanine green (ICG) clearance test was used in a study (Swartz et al. 1974) to demonstrate a hepatic clearance decrease of around 30% during a 3-hour rest at 41°C. A shorter stay in the sauna at 85 to 95°C during 3 to 10 minutes caused a decline of 17% in ICG clearance. However, the drop was not deemed as statistically significant (Vanakoski et al. 1996). Furthermore, a non-human study showed that the central blockade of AT1 receptors significantly reduced the drinking response to short term heat exposure, leading to dehydration (Mathai et al. 2000). On the other hand, dehydration caused by diuretics, mainly thiazides, leads to hyponatremia due to increased oral water intake (Filippone et al. 2020). In situations where the environmental temperature is higher than the core body temperature, sweat production is the primary physiological way to lose heat (Hajat et al. 2010; Sessler 2009). Anticholinergic drugs, especially if

taken by elderly people, can delay or diminish that response due to having impaired sweating as their side effect (Kenney & Munce 2003; Luber & McGeehin 2008). Anticholinergics are a wide group of drugs used for the treatment of many diagnoses, not just psychiatric, that block the action of acetylcholine, a neurotransmitter found in synapses in the central and peripheral nervous system. They reduce heat elimination mainly by interfering with parasympathomimetic mediated sweat secretion, resulting in reduced sweating (Chazova et al. 2013). For all the reasons mentioned above, heatwave periods often require a modification of the patient's base therapy. A reduction, but never complete removal, of the antihypertensive drugs' dose, is often required because of the development of clinically significant hypotension. Therefore, it is recommended to prioritize prescribing calcium channel antagonists, angiotensin-converting enzyme inhibitors and selective beta-blockers (Chazova et al. 2013). Patients on diuretics would require individual daily monitoring of fluid intake and body weight (Smirnova et al. 2019). Because most psychotropic drugs have a substantial impact on body temperature regulation as a result of its numerous effects on the hypothalamus, psychiatric patients are at specifically great risk of developing a heat-related illness, which can lead to heatstroke (Martin-Latry et al. 2007). Some authors even claim that psychiatric patients have three to four times higher incidence of heat-related deaths than the general population (Bark 1998; Bouchama et al. 2007). Having that in mind, two groups of psychiatric drugs, which are very often prescribed, have a significant impact on body temperature regulation: antipsychotics and antidepressants. Studies have shown that schizophrenic patients on antipsychotic therapies have a much lower heat tolerance, with a higher possibility of developing hyperthermic syndromes such as febrile catatonia or neuroleptic malignant syndrome (Hermesh et al. 2000). Antipsychotics have combined anticholinergic and central thermoregulatory effects. They can cause impairment of hypothalamic temperature regulation (Stöllberger et al. 2009) due to its antidopaminergic activity, which elevates the set point of temperature regulation centre (Fijnheer et al. 1995). Moreover, they can also inhibit sweating (Kwok & Chan 2005). Both of these mechanisms lead to increased body temperature and higher risks of heat-related illnesses. While atypical antipsychotics have, in general, proven to cause less antidopaminergic side effects compared to typical antipsychotics, there have been cases reported where heatstroke occurred during atypical antipsychotic therapy, specifically with clozapine (Kilbourne et al. 1982). Both of these groups should be used with great care during hot weather, mainly because heat-related illnesses can easily be mistaken for neuroleptic malignant syndrome or vice versa. Misdiagnosing can have fatal results. While both of these entities are associated with fever and altered mental status, neuroleptic malignant syndrome is characterized by extrapyramidal symptoms such as muscle rigidity. Still, during heatstroke limb flaccidity occurs more often, combined with dry skin and hypotension (Berman 2011). Besides antipsychotics, antidepressants also have a significant impact on thermoregulation. Most recent NHS Digital data show that the number of prescriptions for antidepressants in England has almost doubled in the past decade (Iacobucci 2019). According to 2017 statistics, one in six people in England was prescribed an antidepressant and more than 4 million people were long term users, placing antidepressants as fourth on the list of most prescribed medications in England (National Health Service 2017). Antidepressants are a broad group of drugs, including SSRIs, SNRIs, TCAs, MAOIs and atypical antidepressants. SSRIs and SNRIs are the most often prescribed groups, but also the most unsafe for usage during hot weather, because of the serotonin's double effect on the body's temperature regulation (Sheard & Aghajanian 1967). Researchers have shown that the release of serotonin in the anterior hypothalamus stimulates the cholinergic heat production pathway. Therefore, inhibiting serotonin reuptake will increase heat production. Additionally, serotonin inhibits dopaminergic heat loss pathways, resulting in excessive heat acumination (Epstein et al. 1997). This is especially important for patients who use anticholinergic or antidopaminergic medications along with antidepressants.

CONCLUSION

In conclusion, heatwave periods are not to be taken lightly and should be approached with utmost caution while prescribing therapy. It is of critical importance to inform and educate vulnerable populations early in the season and promote proper hydration throughout the periods when temperatures exceed local averages (Liss & Naumova 2019). Finally, it appears that the future, when heatwaves will become more intense, frequent and longer lasting (Meehl & Tebaldi 2004), represents a new challenge not just for practicing medical professionals, but also for the patients and the pharmaceutical industry.

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Contribution of individual authors:
Tin Sklebar conducted the literature search, critically refined relevant articles, shaped the main ideas of the work and co-authored the article. Kristian Dominik Rudez and Lorena Karla Rudez co-authored the article,

contributed to selecting relevant references and shaping the main ideas of the article. Prof. Robert Likic, MD, PhD (guarantor) made the main conception of our work, critically revised it and approved the final version.

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