Title: The long journey of a benzodiazepine

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Abstract:

Medications make up 12-25% of health care's greenhouse gas emissions production. By utilizing a life cycle analysis approach, this article lays out each step of production and disposal and estimates the global journey of a generic clonazepam pill. Generic clonazepam was selected because it is a commonly prescribed medication and is often linked to deprescribing initiatives due to its potential patient harms. A visual map was created to illustrate each step of the medications life cycle, from Active Pharmaceutical Ingredient (API) mining to patient usage. Our findings demonstrate that health care prescribing practices have tangible environmental impacts and manufacturers should continue to invest in operational streamlining to reduce their greenhouse gas emissions. Overall, there is a need for clinicians and leadership to become more aware of the connection between medication prescription and climate change so that healthcare systems can start to reduce its emission production.

Introduction

The National Health Service (NHS) in England published a carbon footprint assessment of the various greenhouse gas (GHG) emission hotspots within the healthcare system, identifying that production of medications accounts for 12-25% of GHG emissions (1–3). Interestingly, this is greater than the total GHG emissions produced by healthcare buildings, energy, and transportation combined (4). Similar assessments carried out in the United States have also cited pharmaceuticals as a top GHG contributor within the healthcare sector (5). Furthermore, research indicates that the pharmaceutical industry's emissions intensity is approximately 55% higher than emissions from the automobile industry (6). Despite these notable metrics, there remains a lack of transparency and understanding of GHG emission production throughout the supply chain of pharmaceuticals.

There have been movements to optimize and reduce unnecessary medication usages, with the intention of reducing carbon emissions to minimize environmental harm (7). A 2021 review by the United Kingdom's (UK) Department of Health and Social Care estimated that at least 10% of prescription items in UK primary care were unnecessary (7). Specifically looking at the commonly prescribed medication class, benzodiazepine, it has been estimated that 30.6 million adults in the United States (10.5% of the US population at the time of the study) reported benzodiazepine use in the year 2015-2016 (8). Within this population, it has been reported that 2.2% of users have misused a benzodiazepine prescription. Additionally, the quantity of benzodiazepine prescriptions filled each year between 1996-2013 increased from 1.1 kg to 3.6 kg lorazepam-equivalents per 100,000 adults (8). Stressors related to the COVID-19 pandemic are speculated to have increased the prescribing and misuse of benzodiazepines (8,9).

Reducing overprescribing does not compromise treatment effectiveness and yields several benefits for patients, the environment, and society as a whole. For instance, reducing overprescribing is as effective as conventional care strategies for managing hypertension in the elderly (10). Similarly, initiatives like the NHS Long-Term Plan "Choose Wisely" in England (11), "Realistic Medicine" in Scotland, "Less is More" in the United States, and “Choosing Wisely Canada” aim to reduce overprescribing, in addition to unnecessary tests and treatments for patients, thereby reducing the associated potential harms and resource consumption (12). Due to these programs, many clinicians, policymakers, and medical learners are informed, in general, of the potential harm of unnecessary prescribing on patients, and most can appreciate the harm to the environment.

However, the exact process of assessing GHG emissions for pharmaceuticals and chemicals is not well known, nor is there an established approach to this (13). A more in-depth understanding of a medications life cycle may assist these audiences in better appreciating the environmental consequences of pharmaceuticals, and in directing future prescription practices and healthcare emission reduction related policies.

In this article we delve into clonazepam, a frequently prescribed benzodiazepine, and provide an exploration of its life cycle as well as investigate the global scope of its supply chain. To clearly depict the production and distribution process of this benzodiazepine, we have created a map that illustrates its journey from cradle to grave. Our objective is to shed light on the often overlooked, intricate, and unexpected environmental impact left behind by the creation of a single medication. We have highlighted the extensive cradle to grave journey so that the pharmaceutical industry will re-think their supply chain if they want to address their large carbon footprint. Also, with our results, health care providers, healthcare leadership, and policymakers will be able to recognize the potential harms of overprescribing from not only a patient perspective, but a planetary one as well.

Background:

Climate change is a grave and pressing issue that has profound impacts on human health and overall well-being. The World Health Organization (WHO) estimates that between 2030-2050, the impacts of climate change, such as land degradation, urbanization, and biodiversity loss, will lead to health issues including undernutrition, exacerbation of chronic respiratory illness, heat stroke, and changes to vector-borne disease patterns (e.g., malaria). The WHO anticipates this will result in 250,000 additional deaths globally per year (14,15). Additionally, there are rising levels of climate anxiety among children and young adults across the world (16). The healthcare sector plays a pivotal role in responding to the health impacts of climate change and thus has a responsibility to be aware of its GHG emission production.

Healthcare system emissions are generated through various avenues, including waste production, energy consumption, direct release of anesthetic gasses, and acquisition of resources in the supply chain (2). In many countries falling under the “Organization for Economic Cooperation and Development” (OECD), such as Canada, US, and UK, healthcare system emissions are responsible for approximately 3-10% of their yearly GHG emissions, excluding anesthetic gas emissions (2,17). With pharmaceuticals contributing up to one quarter of these emissions, there is value in understanding emissions associated with each step of the pharmaceutical production process.

Delving into the pharmaceutical production process will help determine where efficiencies can be implemented to make production more environmentally sustainable (18). "Life Cycle Analysis" (LCA) is a widely accepted tool for assessing the environmental impacts of pharmaceutical products by analyzing the product's entire journey from creation to disposal, often referred to as "cradle to grave" (19,20). LCAs quantify inventory flows, inputs, and outputs using mass and energy balance. They effectively establish a direct relationship between emissions or resource consumption and their impacts on human health, ecosystems and natural resources based on proven causalities or empirically observed interactions providing a strong basis for decision making (21–23).

Multiple LCAs reveal that, in most categories, the highest environmental impacts stem from the supply of essential production materials rather than the resources and energy used in pharmaceutical production. This highlights the critical importance of considering the source of extracted materials for inputs in pharmaceutical manufacturing (24). Moreover, suppliers in each step of the life cycle are located around the world. Materials are shipped back and forth between countries throughout the production process as individual countries specialize in specific steps of production as opposed to the entire production process (25,26).

There are several pathways which can be used to produce a generic medication, one of which may be more energy and resources efficient than the others pathway. However, there is currently a lack of information available for the health care industry and, potentially, manufacturers to know which has the least environmental impact. Despite the usefulness of LCAs in understanding pharmaceutical environmental impact, the pharmaceutical sector has been found to conduct inadequate assessments (27). Notably, methodological inconsistencies within pharmaceutical LCAs result from challenges with limited availability of inventory data due to confidential synthesis routes and complex supply chains (20,27). Albeit, in recent years the pharmaceutical industry has begun to adopt sustainable manufacturing practices. The utilization of green chemistry and engineering principles to reduce environmental footprints in manufacturing has become more mainstream within the industry (28,29). Additionally, clinicians are beginning to learn more about the environmental impacts of their prescribing practices as well as emissions related to healthcare systems in general (7). Emphasizing the global scope of production will contribute to these discussions and may influence how medications are produced and prescribed.

To complete a full LCA, an understanding of various components making up the manufacturing and distribution processes, such as GHG production, energy usage, vehicle usage for shipping, and chemical components, is required. However, since the supply of essential production materials has the greatest environmental impact in pharmaceutical production, our assessments will focus on the global supply chain of the materials and will take a LCA approach rather than completing a full LCA. Additionally, this article is intended for a medical audience with the objective of educating readers on the components of production and explaining the associated environmental impacts, thus it is our determination that the defined scope of our work would allow us to do this without completing a full LCA.

Methods:

Determination of clonazepam as a focus

To portray and understand the life cycle of a benzodiazepine, we selected one specific medication to investigate based on the information available within this class. Clonazepam, belonging to the benzodiazepine class of medications, finds application in the treatment of various medical conditions such as insomnia, anxiety, and seizure disorders (30). It is commonly prescribed as a second line treatment and it is among one of several classes of medications that is commonly overprescribed by clinicians (31).

The practice of polypharmacy, involving multiple medications, can be detrimental to patients, financially burdensome for healthcare systems, and harmful to the environment (7,32). Benzodiazepines are widely used in both acute phases of patient care and during long term treatment (33). A recent study found that long-acting benzodiazepines, such as clonazepam, were one of the most commonly prescribed polypharmacy and potentially inappropriate psychotropic (PIP) medications for older adults with a psychiatric illness (34).

Despite being a commonly used and prescribed class of medication, the benefits of benzodiazepines must be weighed against a range of adverse effects, including the development of tolerance, dependence, an increased risk of falls, ataxia, memory impairment, and potential links to dementia (34,35). Clonazepam is known to be habitforming, with limited evidence supporting its long-term use (36,37). Furthermore, alternative pharmacological options with lower addiction potential exist. There are also non-pharmacological interventions suitable for addressing clonazepam primary indications of anxiety and insomnia (38,39). Consequently, alterations to how clonazepam is prescribed could potentially reduce GHG emissions within the health care sector without a large degree of negative consequences. Highlighting the environmental impact of this medication will add to the body of research and may practically change how clonazepam is prescribed.

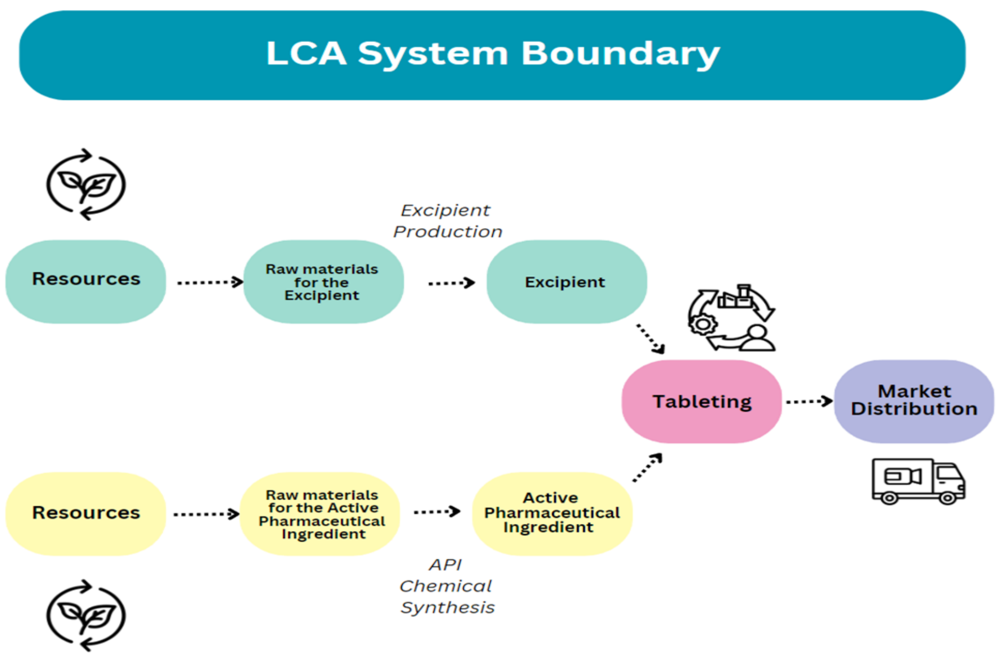
There is limited transparency within the pharmaceutical industry, thus we speculated that an older, more common class of medications (benzodiazepines) would yield more data and related research for this project. Within the benzodiazepine class, we found clonazepam had more accessible information regarding its manufacturing process.

Literature review and life cycle analysis approach

This project started with an analysis of a medication's life cycle and included a literature search to determine the global scope of cradle to grave production. To analyze the LCA of clonazepam we first conducted a literature review to determine the basic components of a standard pharmaceutical LCA. This involved understanding the life cycle's system boundaries (system boundaries define each production cycle step, marked by the intersection of technology systems with nature, geography, time, and distinctions from other technical systems), and determining the most likely points of production that could be included in a global representation.

Every medication consists of two major significant ingredients: Active Pharmaceutical Ingredients (API) and Excipients. APIs are pharmaceutically active drugs that generate a desired pharmacological effect (cure, treat, prevent disease). Excipients are pharmacologically inactive substances generally used as carriers (facilitating absorption, excretion, flowability, preventing denaturation) of the API in the drug. it was determined that the system boundary of an LCA consists of several significant parts, namely (1) API production, (2) excipient production (De Soete et al., 2013; Ott et al., 2016), (3) chemical synthesis and formulation, including testing (Alder et al., 2016) (4) market distribution including packaging and costs (5) customer consumption and disposal form (5,18,40–42). Figure 1 shows the LCA system boundary from the raw material extraction of the excipients and API to drug distribution. This process will be used as a basis for our model of clonazepam's production journey.

Fig 1.
LCA system boundary



Next, we conducted a literature review on information available related to manufacturing of clonazepam and/or benzodiazepines in general. This involved using search databases and platforms such as PubMed and Google Scholar with keywords related to pharmaceutical manufacturing, emission production, distribution, and procurement. We also assessed industry reports, gray literature, pharmaceutical databases (ie.PharmaCompass), export records, and market reports. This allowed us to determine geographical hotspots and understand how production spanned the globe. Lastly, we reached out to pharmacies in the Hamilton, Ontario, Canada area (location of the research team) and inquired about where their shipments were coming from. With this information, we were able to confirm some of the results we had identified about the Canadian supply chain.

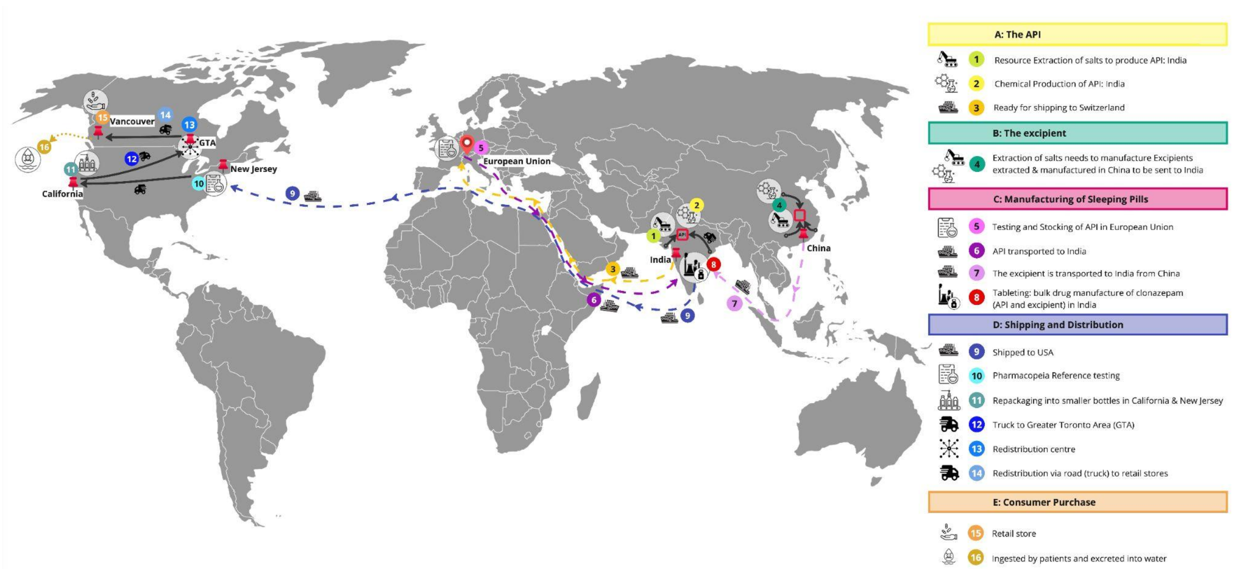
A limitation of our research was manufacturer specific data. Most medication manufacturers do not publicly disclose their primary data as this is considered confidential business information and proprietary (25). Throughout the course of our research, several attempts were made to contact clonazepam and benzodiazepine manufacturers directly via email and inquiries on website portals. We explained that we were researchers authoring an article about the clonazepam supply chain and were looking for feedback and confirmation. Companies contacted include: Teva Pharmaceutical Industries Ltd., Aurobindo Pharma USA, Inc., Accord Healthcare Inc., Actavis Generics, Prinston Pharmaceutical Inc., Hoffmann-La Roche Ltd., Rubicon Research Pvt. Ltd., and Sandoz Group AG. There was a poor response rate to our emails and inquiries, and any responses received harbored limited information that did not provide additional insight beyond the publications included in our literature review.

Finally, we contacted industry professionals and leadership via email, LinkedIn messages, phone calls, and informal in-person discussions. These professionals included pharmaceutical company vice-presidents, retired professors who previously researched pharmaceutical supply chains and manufacturing, supply chain insurance company, and a sustainable supply chain consulting company. Little to no additional information was provided from these investigations. We also contacted the Clinton Foundation due to their previous work in medication processes, who confirmed the legitimacy of the API process that we determined from our literature review.

Results

The environmental impacts of producing and manufacturing clonazepam, including the intensive processes of API and excipients extraction, were mapped to highlight the cradle to grave process of clonazepam (Figure 2). The LCA approach was employed to determine the significant regional contributors to the environmental footprints between API chemical synthesis, excipient formulation, drug manufacturing, and regional distribution, without accounting for GHG emissions at each step. Due to the lack of manufacturer specific data available, Figure 2 displays an estimation of the general global journey of clonazepam, starting in India and China and ending in Vancouver, Canada (this location was selected to illustrate the potential global scope of the journey). While there are many sites involved in the manufacturing of clonazepam that are not specifically highlighted in this figure, we have depicted a plausible production process that highlights key and central locations throughout the life cycle as well as emphasized its potential global breadth.

Fig 2.



The journey of a pill starts with the extraction of salts to produce the API and the chemical production of the API. The API chemical production involves extensive resource consumption including use of chemicals, electromechanical power, heating/cooling media, inert gases, cleaning agents, transport, and treatment. Additionally, within each of these consumption steps there is an associated supply, treatment, and disposal process (41).The global centers for clonazepam API salt extraction and chemical production are India and China (25). As of 2019, China and India contributed approximately 44.8% of the global API production market (25).

Quality testing and stocking for APIs are typically completed outside of India and China - namely in the European Union, with some locations, for example, being in Switzerland (43–45). Once this step is completed, the product is shipped back to India for the final manufacturing stages. For APIs to be suitable for consumption on their own, various additional ingredients (excipients) are formulated into the final product (46). China holds a large market for excipient extraction, with more than 400 excipient manufacturers located in the country (25,47). Excipients are shipped from China to India and are combined with the APIs to complete the manufacturing of clonazepam (25,26). From there, the pills are sent to global markets for tableting and Final Dose Form (FDF), also referred to as Final Dose Product, manufacturing, and regional distribution (48). Stock of clonazepam is also held within European countries, such as Switzerland, for future distribution (49).

For our map, we have chosen a final consumer in Vancouver, Canada, thus the pills are shipped to North America. Due to the light weight, small size, and resilience of solid pills, they are generally shipped in large containers such as tank rail cars, by air or shipping freight containers (25). The New Jersey area is one of North America's largest intake points for these shipments. This area holds the greatest pharmaceutical manufacturing concentration within the US for FDF manufacturing. These FDF locations are also closely located to US Food and Drug Administration (FDA) headquarters (25). Furthermore, the US is the global leader in FDF manufacturing, holding 41% of global sites (25). Of note, this could indicate to customers outside of North America that their pills may require an additional trans-Atlantic journey after FDF manufacturing is completed. For our chosen Vancouver consumer, once the FDF is manufactured in New Jersey, the pills are shipped to and repackaged in California for North America-wide distribution (50). Upon reaching the Canadian market, the medications are sent to industry clusters within metropolitan areas, typically within the Greater Toronto Area (The GTA is home to 6 of the top 10 pharmaceutical companies in Canada, making up 30.6% of market share) (51). The medications are then shipped to individual distribution sites, such as pharmacies and hospitals, for patient use.

Our map depicts the extensive, global journey of the clonazepam pill culminates with its consumption in Vancouver. The life cycle of a pill does not completely end in its consumption. It is important to recognize that waste production and disposal of pharmaceuticals are additional key components of an LCA. Metabolites of the pill are excreted into users' urine, and if they enter aquatic environments, they may have lasting environmental impacts (52).

Discussion:

The results of this investigation reveal an extensive global effort to produce the commonly prescribed benzodiazepine pill, clonazepam. Production can begin on one side of the world and finish on the other; nations specialize in various components of production, and often ship materials back and forth several times throughout the entire process. This is problematic in a world facing the detrimental impacts of climate change as each step in a medication's life cycle is associated with significant GHG emissions, resource consumption, and energy usage. In directing prescribing decisions, in addition to formulating policies around pharmaceuticals and their procurement processes within the health care sector, it is crucial for leadership, policy makers, and prescribing clinicians to actively consider the expansive global journey involved in pharmaceutical production.

India and China were identified as hubs of production. They each hold specialized processes and rely on shipping between each other for the final product to be formulated. The use of cargo ships is often seen as an environmentally efficient means of transporting bulk goods, yet the shipping industry makes up approximately 2.2% of global emissions (53). Thus, targeted interventions requiring India and China to streamline transportation and reduce unnecessary shipments of materials back and forth between each country could have a significant impact on reducing the carbon footprint of medications. Furthermore, The International Maritime Organization has set a goal to reduce GHG emissions related to international shipping by at least 50% by 2050 when compared to 2008 measurements (53). Creation of country specific supply chains and/or a reduction in the practice of shipping materials back and forth during manufacturing would contribute to this GHG emissions reduction target.

Challenges within the medical supply chain, namely political tensions and global economic disruptions, may be catalysts to domestic supply chains becoming more standard in the industry (48,54). Growing tensions between the US and China are causing industry to reevaluate the low cost of China's manufacturing vs. the potential impediments to their future supply chain development. Moreover, since the COVID-19 pandemic and recent delays and disruptions to global shipping, there have been concerns that geopolitics will impact the future pharmaceutical market (55). Reducing shipments between countries during each stage of production may lessen geopolitical concerns, introduce resilience to the system, and reduce emissions associated with production (45,48).

Overprescribing, polypharmacy, and misuse of medications are also issues within the healthcare sector which require a green lens. It has been found that physicians will alter their prescribing practices when they are educated on the emissions related to medication. For example, in their analysis of GHG emissions associated with metered-dose inhaler prescriptions, Gagné et al., found that understanding the carbon footprint of the inhalers may have been a powerful motivator and incentivized physicians to be more aware of their prescribing and diagnostic actions (56). Moreover, as we have mentioned in the introduction, there are many guidelines and algorithms available that provide a structured approach to safely deprescribe benzodiazepines, while mitigating the risks associated with its long-term use. Maintaining prescriber education on the environmental impact of pharmaceuticals, importantly ones that are overprescribed and where there are safe and appropriate non-pharmaceutical alternatives, is a tactic that could influence decision making and prescribing practices (57). By integrating planetary health considerations into prescribing practices, healthcare professionals can further optimize patient care while minimizing environmental impact.

Clonazepam brings valuable insight into current prescribing practices and is a medication that clearly shows that alternative practices can be utilized without harming quality of care in many cases. There are various options for moving patients away from this medication, such as enrolling patients in therapy or sleep clinics, reducing long-term prescriptions, and altering titration schedules (37). For example, a study by Tannenbaum et al. (2014) demonstrated the effectiveness of a pharmacist-led intervention in reducing benzodiazepine use among older adults, resulting in improved cognitive function and reduced falls (58). Visual tools, such as figure 2, illustrate the vast scope of production and can help articulate why alternative approaches are necessary to lessen the GHG emissions of health care.

There are equity and social justice components of a medications life cycle that should also be considered in prescription decision-making. Impacts of climate change worsen socio-economic disparities and disproportionately harm already vulnerable communities, notably Indigenous, Black, elderly, and low-income populations (59). Health inequities, particularly in these vulnerable communities as well as patients with chronic diseases, are also amplified (59). Moreover, our map illustrates a large portion of transportation and production occurring in the global south, meaning those countries are dealing with the direct emissions and other pollutants (e.g., wastewater discharge) of production more so than the consumers in North America (60). Therefore, thoughtful prescribing with an equity lens can further inform sustainable changes throughout the supply chain and should be integrated into a clinician's duty of reducing patient harm.

The pharmaceutical and healthcare industries are starting to shift their practices to be more sustainable and transparent. Innovations and new technologies are being utilized in the pharmaceutical formulation industry to address resource consumption in the formulation and manufacturing (41). Further, LCAs are increasingly used within the pharmaceutical industry as this form of analysis sheds light on supplier data and reduces time and cost stressors during drug discovery and development (61). In a Deloitte report (2021), it is suggested that many pharmaceutical companies are taking the initiative to implement sustainable practices with a goal of net zero emissions, but better data management practices in addition to increased sharing of efficiencies and success stories is needed for these goals to be meaningfully met (62). This progress, while imperfect, demonstrates that the pharmaceutical industry is ready and willing to make changes (63). Leadership and pressure from the healthcare sector is needed to drive these changes forward and ensure they are impactful.

The NHS is a leader in sustainable health care and often pilot initiatives that are taken up by other health systems around the world (64). They are working to ensure their suppliers are actively decarbonizing their processes in their NHS supplier engagement program (65,66). Within their net zero road map, by 2027 all of their suppliers are required to publicly report targets, emissions, and publish a Carbon Reduction Plan, and by 2028, they will have requirements to oversee the provision of carbon foot printing for individual products supplied (66). This type of leadership in every country, along with changes from the manufacturers and deprescribing initiatives are urgently needed if we are going to address the climate change impact of health care.

Future research should focus on a full and wholesome LCA of a pharmaceutical. Understanding the emissions and other environmental impacts of each system boundary will assist the pharmaceutical industry in advancing their sustainability initiatives. Additionally, further research into how sustainability education impacts prescribing practices could be investigated to inform and improve implementation practices of related policies. Interventions including medication reviews and education to optimize prescriptions upon hospital admission may also promote more sustainable prescribing while reducing harms and medication burdens on patients (67). Lastly, a deeper dive into a medications local supply chain and movements within a hospital setting to determine bottlenecks, waste, and emissions would be an interesting addition to the research included in this paper.

Limitations

The pharmaceutical industry currently lacks transparency throughout the supply chain, making it challenging for outside researchers to capture the full GHG output for a medication's entire journey (48). We were limited in the number of resources available to the research team as well as insight from the manufacturers themselves. It would be helpful for future research to collaborate with the industry to develop a complete LCA of clonazepam and other highly prescribed pharmaceuticals. Ultimately, the health care sector needs to understand the full footprint of each medication, so that prescribers can choose the option which is best for patients and the planet (67).

An additional limitation for this project was funding. Often industry and market reports are only available by purchase and are expensive. Future researchers should consider budgeting for these documents in funding requests as they may provide necessary detail on the cradle to grave processes.

Conclusion:

There are many components that inform how medications are prescribed by health care workers, understanding the environmental impacts of medication production and the vast supply chain should be considered when making prescribing decisions. Strategies such as reducing unnecessary prescriptions, optimizing alternative treatments, adjusting titration practices, and enhancing medication monitoring will not only improve patient care, but will also minimize healthcare's environmental footprint, fostering an equitable system centered on patients and communities.

Our map illustrates the global scope of production and highlights the interconnectedness of the countries involved. Policy makers, hospital leadership, and pharmaceutical manufacturers can reduce health care GHG emission by lessening the global scope of production and, potentially, implementing regional supply lines. This would also limit production and shipment delays as geopolitics and supply chain interdependence would then have fewer impacts throughout the manufacturing and distribution. In order to get to net zero, all stakeholders have a significant role to play.

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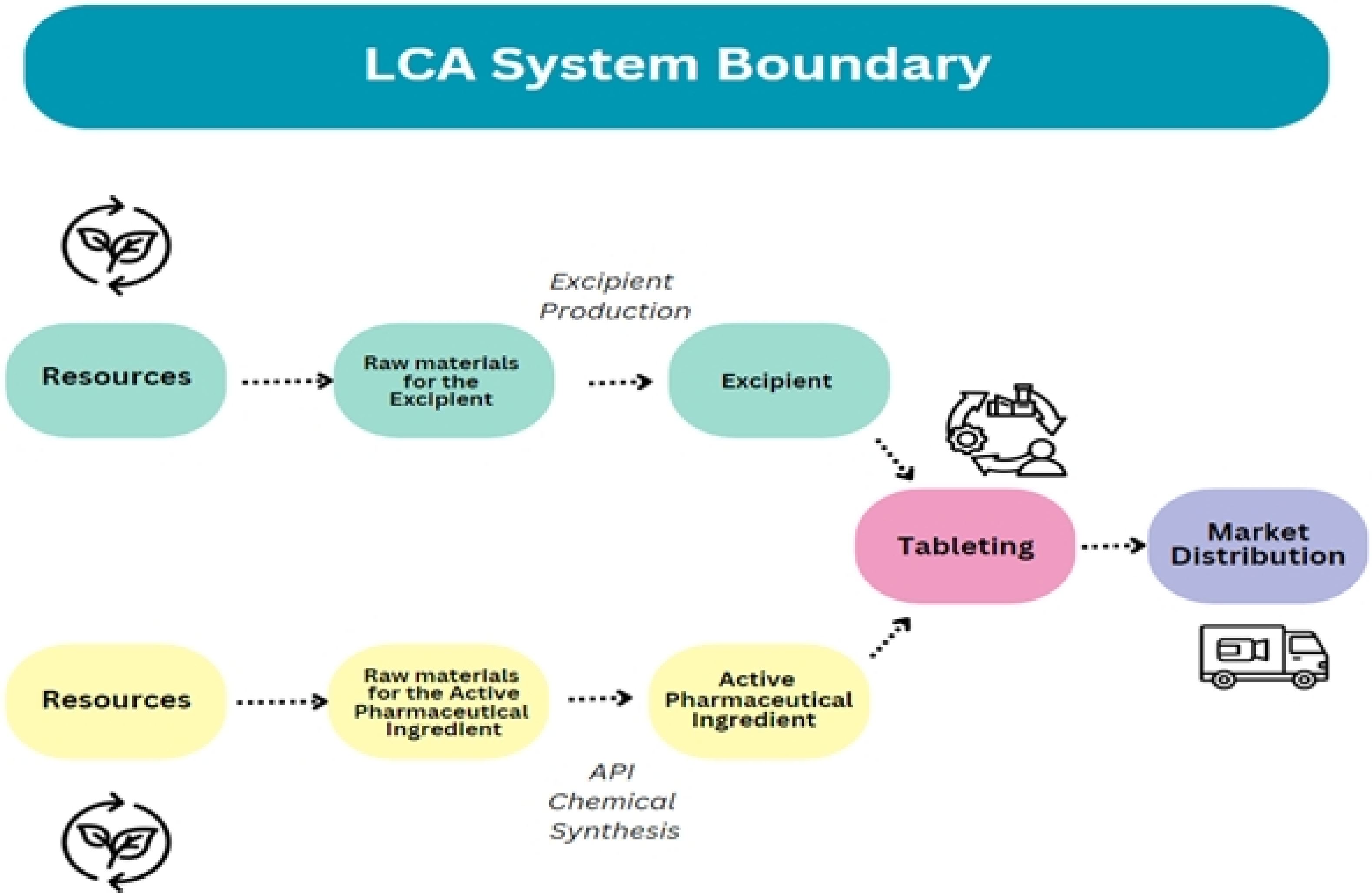
LCA System Boundary
Excipient Production
Resources
Raw materials for the Excipient
Excipient
Tableting
Market Distribution
Resources
Raw materials for the Active Pharmaceutical Ingredient
Active Pharmaceutical Ingredient
API Chemical Synthesis

Figure 1

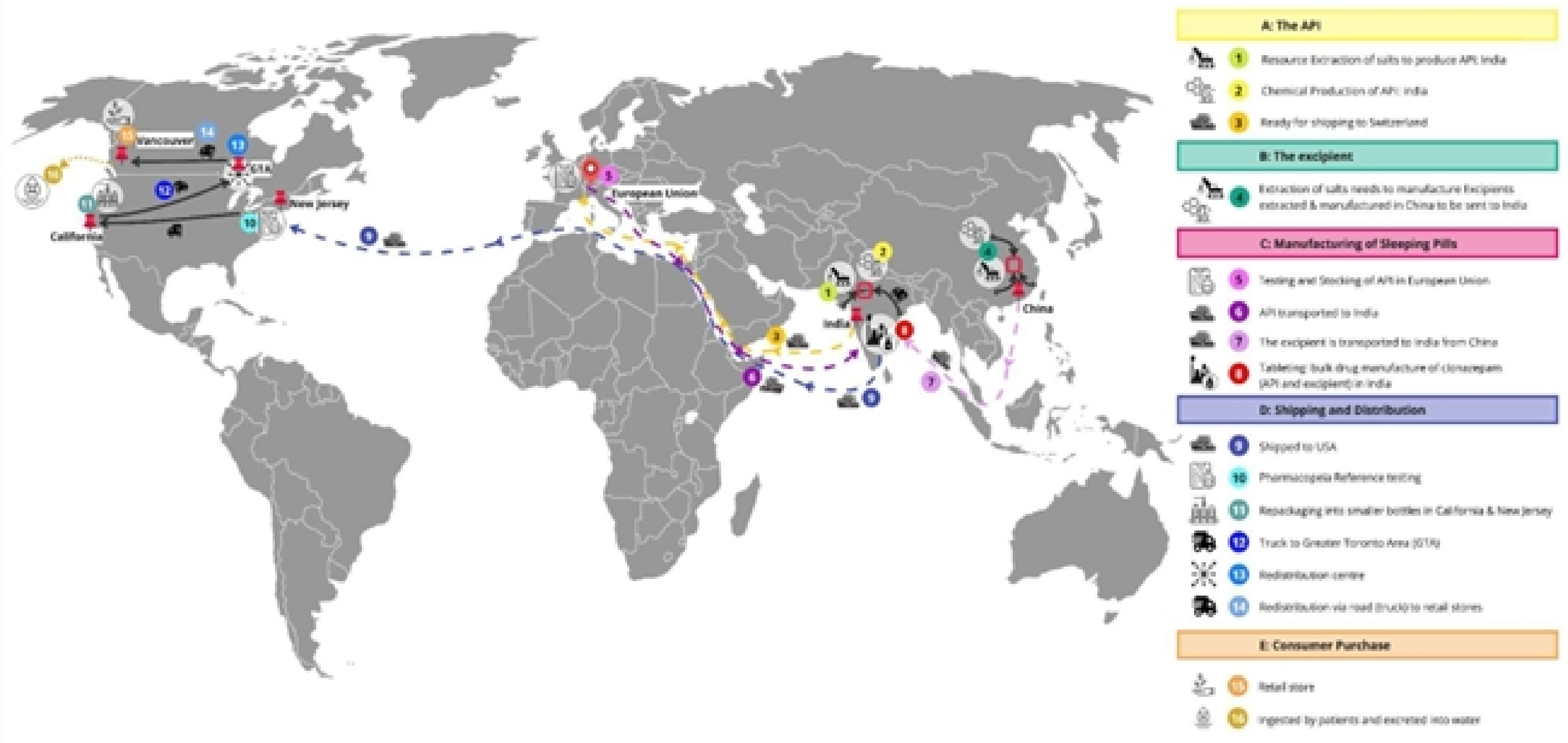
Vancouver
G.T.A.
New Jersey
California
European Union
India
China
A: The API
Resource Extraction of salts to produce API: India
Chemical Production of API: India
Ready for shipping to Switzerland
B: The excipient
Extraction of salts needs to manufacture Excipients extracted & manufactured in China to be sent to India
C: Manufacturing of Sleeping Pills
Testing and Stocking of API in European Union
API transported to India
The excipient is transported to India from China
Tableting: bulk drug manufacture of clonazepam (API and excipient) in India
D: Shipping and Distribution
Shipped to USA
Pharmacopeia Reference testing
Repackaging into smaller bottles in California & New Jersey
Truck to Greater Toronto Area (GTA)
Redistribution centre
Redistribution via road (truck) to retail stores
E: Consumer Purchase

Figure 2