Case study

Structured Benefit-Risk Assessments: *An Illustrative Case Study of Paracetamol*

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ABSTRACT

This paper aims to provide an overview of the steps in developing a structured benefit-risk assessment, along with a simple, salient, and timely example of its implications. Using the time-tested, non-prescription drug paracetamol (a.k.a. acetaminophen) as an example, we demonstrate the fundamental role a well-structured benefit-risk assessment may play in clarifying the safety profile of even well-established medicinal products. The benefit-risk balance assessment performed by drug manufacturers and others involved in keeping drugs on the market is integral to a non-stop drug safety assessment continuum throughout a product's lifecycle. This provides further reassurance that, as the world grapples with new diseases, pharmacovigilance systems with robust tools such as structured benefit-risk assessments can evolve and adapt by developing essential preventive and mitigative strategies. All these examples and practices contain the through-line of consideration for the protection of public health, a foundational cornerstone of pharmacovigilance practice. While a wealth of information may be explored on each aspect of the presented topics, the authors aim to give even those readers with only minimal background in pharmacovigilance an appreciation for the value of structured benefit-risk assessments.

KEYWORDS

Pharmacovigilance; Benefit-risk assessments; Paracetamol (Acetaminophen); COVID-19

INTRODUCTION

Paracetamol [a.k.a. acetaminophen, a.k.a. N- acetyl- p-aminophenol (APAP)] is an old medication that has been used to treat individuals with mild to moderate pain and fever as far back as the 1870s. (1,2) Today, paracetamol is one of the drugs included in the World Health Organization's (WHO) list of essential emergency medicines (3). It is a generic medication with brand names including Tylenol®, Calpol®, and others. Paracetamol can be used as a stand-alone medication or combined with other drugs such as aspirin, caffeine, and ibuprofen, which has been shown to increase its efficacy in some indications. (4,5) While these combination therapies raise concerns over the potential for additively or synergistically increasing unwanted effects, studies show that such combination therapies appear well-tolerated. (6,7) As one of the only drugs currently approved for use in managing fever and pain during pregnancy as well as for indications that commonly occur in patients of all ages, (8) paracetamol provides a useful example covering many aspects relevant to drug safety assessments including consideration during use in special patient populations.

Although paracetamol is an old product, the understanding of its safety profile has continued to evolve with the development of pharmacovigilance (a.k.a. "drug safety") tools such as structured benefit-risk assessments (sBRAs). During the 1960s, pharmacovigilance monitoring practices and standards were significantly enhanced to include new monitoring and reporting requirements in the United States (US) and Europe. (9) By that time, with nearly a century of clinical use and decades of commercial availability, paracetamol had become a widely-used drug that was generally regarded as safe and effective. (10) The continued improvement of pharmacovigilance regulatory evaluations, including access to new technologies and enhanced access to pertinent data, further prompted the identification of previously unrecognized aspects of paracetamol's safety profile, especially in the late 1970s. The following overview of some key regulatory and safety

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milestones is not intended as a comprehensive review of the product's history but is rather aimed at helping to highlight some important ways in which pharmacovigilance systems have helped in the evolution of the understanding of the benefits and risks of paracetamol.

PARACETAMOL'S REGULATORY AND SAFTY MILESTONES

In 1977, the US Food and Drug Administration (FDA) codified the conditions under which over-the-counter (OTC) internal analgesic, antipyretic and anti-rheumatic drugs could be generally recognized as safe and effective without being misbranded. This included a warning not to exceed the recommended dose due to paracetamol products' risk of severe liver damage. (11) In 1998, a restriction was placed on the pack sizes for paracetamol sold OTC in the United Kingdom (UK). (12) That same year, additional warnings regarding the risk of liver damage when combined with alcohol were required by the FDA for several OTC analgesics. The FDA later recognized unintentional overdose with paracetamol as a risk for the development of serious hepatotoxicity. (13) Studies on the impact of pack size reduction more than ten years after the new legislation have shown a marked decrease in paracetamol-related deaths, liver transplants, and the number of tablets consumed in overdoses. (14)

In 2002, the FDA further evaluated the risk of liver toxicity in overdose, which indicated that the product was a leading cause of liver injury after accidental and intentional overdose. Although paracetamol was calculated at the time to have potentially contributed to around 100 deaths per year in the US, this figure does not reflect the overall toll on morbidity due to liver failure: it would certainly have been higher if not for life-saving procedures such as liver transplantation. The evaluation also identified potential risk factors that may contribute to hepatotoxicity during the use of paracetamol, such as the combined use of multiple products and underlying liver diseases. This led to the implementation of several risk-minimization measures, including changes to the packaging and additional warnings on both OTC and prescription products containing paracetamol, as well as consumer and health provider educational campaigns. The analysis concluded that these changes were necessary to maintain a positive benefit-risk balance (BRB) for paracetamol-containing products. (15) Additional changes to the product label for paracetamol were required in 2010 and 2011 regarding the risk of liver injury and information on allergic reactions. (16,17) In 2011, the US FDA announced that it would ask drug manufacturers to limit the strength of paracetamol in prescription drug products to 325 mg per tablet by 2014. Such products are generally combinations containing opioid analgesics such as hydrocodone (Vicodin®, Lortab®) and oxycodone (Tylox®, Percocet®). (16) This limitation was intended to reduce the risk of inadvertent hepatotoxicity. An early assessment of the mandate's effect suggested no appreciable decrease in events of inadvertent hepatoxicity. (18) This outcome may have been attributable to the decreased bioavailability of paracetamol in opioid-containing combination products. (19)

In 2013, the US FDA and the European Union (EU) Pharmacovigilance Risk Assessment Committee (PRAC) first took note of several cases of Stevens-Johnson Syndrome (SJS), a severe cutaneous adverse reaction (SCAR), which had been described in the medical literature. A subsequent review of all cases of SCARs in patients exposed to paracetamol reported to the agency from 1969 through 2012 identified more than 100 patients, most of whom had used single-ingredient paracetamol products. These findings ultimately led to the inclusion of the SCARs SJS, toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) in the product labeling as a risk minimization measure for paracetamol-containing products in both the US and the EU. (20–23)

In 2014, a signal[2] was raised by the PRAC for paracetamol and drug exposure in pregnancy; the results of a large cohort sibling study indicated that paracetamol exposure in utero of more than 28 days in duration was associated with adverse neurodevelopmental outcomes. (25) Due to the study's limitations, the PRAC considered that further investigation was required to establish a potential causal association with paracetamol exposure. (26) After an extensive review of the data available from literature, preclinical studies, epidemiological studies, and Marketing Authorization Holders, the PRAC concluded in 2019 that the data on this topic was inconclusive. The PRAC also required that the state of the scientific data on this topic be reflected in the updated wording of the product labeling. (27)

In 2016, the Swedish Medicines Agency notified the PRAC of data from pharmacokinetic and clinical analyses indicating that the standard treatment protocols for overdose from extended-release paracetamol were inadequate. This led to a referral under Article 31 of Directive 2001/83/EC, a review of the BRB of the extended-release formulation. (28,29) In 2017, the PRAC and the Co-ordination Group for Mutual Recognition and Decentralized Procedures – human (CMDh) agreed that the risks of modified or prolonged-release paracetamol outweighed the benefits, a finding supported by the European Commission (EC). As a result, modified and prolonged-release paracetamol was suspended from European markets in 2018. Return of these products to the European marketplace would be possible only if Marketing Authorization Holders could provide evidence of "...appropriate and practical EU-wide measures to help prevent overdose with these products and adequately reduce its risks." (30)

In 2021, a consensus statement endorsed by an international assembly of more than 90 scientists, clinicians, and public health professionals, claimed that pregnant women should be cautioned at the beginning of pregnancy

[2] "A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine, and that warrants further investigation." (24)

to avoid using paracetamol and that if it is medically necessary, they should use the lowest effective dose for the shortest time possible. This recommendation was based on a comprehensive review of epidemiological and interventional studies published over 25 years regarding exposure to paracetamol during pregnancy. The authors concluded that the evidence indicated a risk of developing attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and abnormalities of the male and female reproductive systems after in-utero paracetamol exposure. (31) While we echo those authors' opinion that the information presented in their position paper warrants the attention of health authorities (HAs) and Marketing Authorization Holders, we have not yet identified any further recommendations or regulatory actions taken on the basis of that publication.

STRUCTURE BRA FOR PARACETAMOL: KEEPING SAFTY IN PERSEPCTIVE

While benefit-risk assessments were fundamental and addressed during all safety and regulatory milestones for paracetamol, a list of risks from an accumulation of data over the years may not make clear how the BRB of the drug remains positive. This may be where the sBRA plays a key role: it contextualizes the risks by providing cumulative weighted evidence in support of or against the continued use of the product.

Weighed against the evidence for the risks of paracetamol, an sBRA provides detailed information on the drug's efficacy in consideration of available alternative therapies. The sBRA also describes how both voluntary and obligatory risk mitigation strategies help counterbalance the risks associated with drug use. The interplay of these factors may be demonstrated for educational purposes, as shown in Figure 1, where the benefits of paracetamol are shown (on the right) and balanced against the risks (on the left). While this symbolic scale remains tipped to the right (i.e., having a positive benefit-risk balance), the benefits on the right are depicted as being (potentially) offset by any available alternatives, and risk-mitigation strategies offset the risks on the left. This balance is often illustrated in a more formalized manner using an sBRA "value tree" format, as shown in Figure 2.

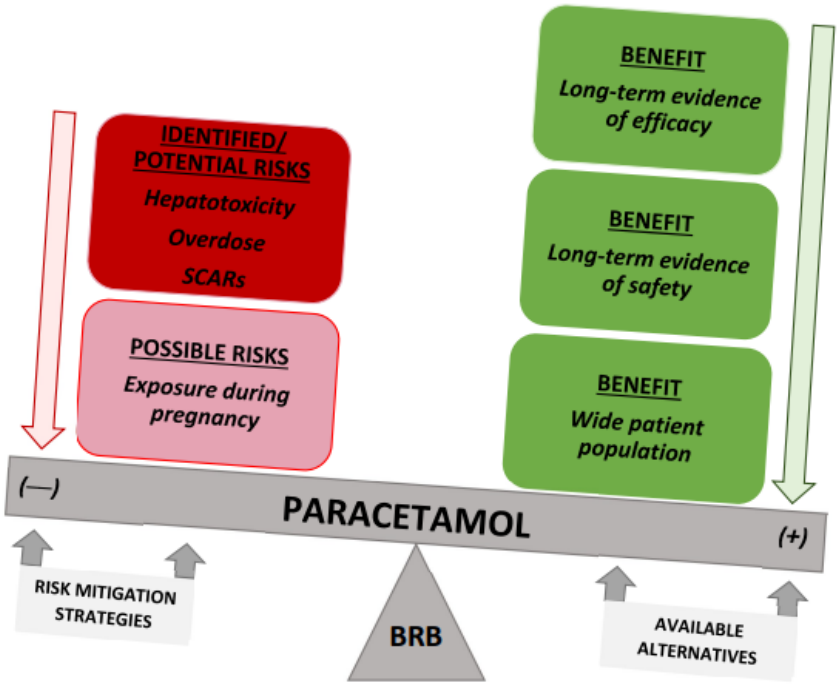

Figure 1. Factors contributing to the sBRA for paracetamol

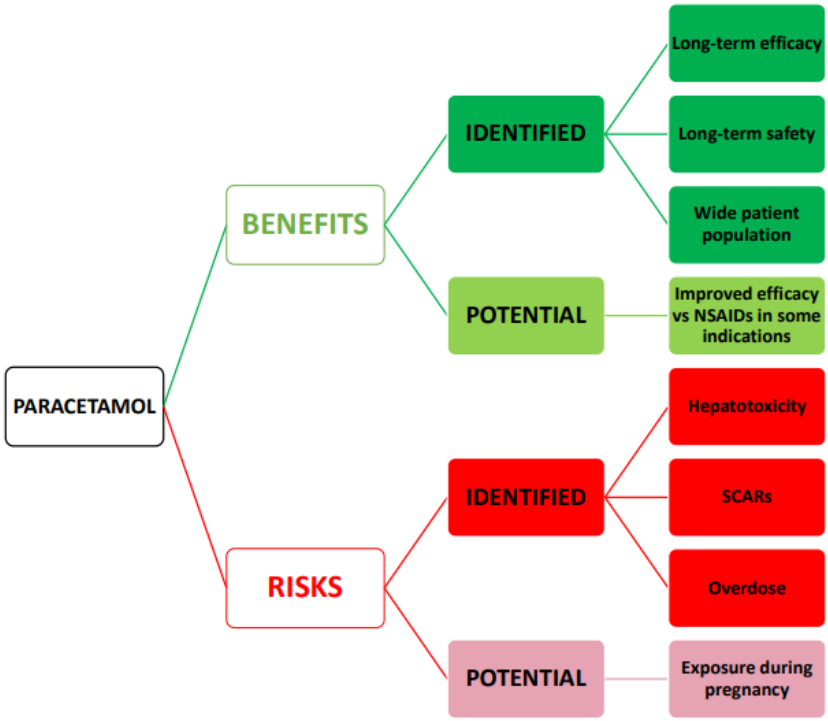

Figure 2. Example value tree presentation of the benefits and risks of paracetamol

Implementing updated labeling for paracetamol is one of the mitigation strategies that has helped offset the risks associated with the drug's use. The rules and guidelines around product labeling are designed to provide thorough and reliable information for patients and prescribers alike. For example, since 1979, the US FDA labeling requirements for drug exposure during pregnancy placed drugs into "classes" (i.e., Class A, Class B…) based on evidence supporting safety during pregnancy. Since 2015, these classes have been phased-out in favor of a more comprehensive description of the available safety information. This effort is intended to avoid misinformmation and allow more informed clinical decision-making. Pregnancy represents just one of the "special populations" to consider regarding a drug's safety profile. Paracetamol is the only drug approved to treat fever during pregnancy, and early pregnancy fever has been linked to neural tube defects. Therefore, avoiding paracetamol use during pregnancy as recommended by the recent consensus statement (31) may have significant implications. Ongoing efforts, including updated labeling, sBRAs, and other routine pharmacovigilance practices, will help ensure that the BRB of paracetamol use in all indications and populations remains positive even as the understanding of the risks continue to evolve.

Updated drug labeling is just one risk mitigation strategy that has helped ensure that the benefits of paracetamol (in consideration of alternative drugs approved for the same indications) outweigh the risks. A salient and timely example of the use of paracetamol in respect of the alternatives arises from the public health crisis created by the opioid epidemic. The risks of opioids appear to have outweighed their benefits at least in some indications in consideration of the available alternative; paracetamol can reduce or eliminate the need for opioids in treating acute pain. This makes paracetamol an important part of the strategy to help mitigate later opioid addiction and abuse risk. (32)

Per our previous publication (33), an sBRA should present key evidence for a medicinal product's benefits, risks, and uncertainties that may inform regulatory decisions. This approach is supported by the US FDA 2021 guidance on benefit-risk assessments. (34) As shown in Table 1, the content of an sBRA should include product details, an overview of the drug's mechanism of action, benefits evaluation, risk evaluation, benefit-risk analysis evaluation, and a summary of key factors that contribute to the benefits and risks. Table 1 below provides the recommended format and example content for an sBRA using paracetamol as an illustrative case.

Table 1. Recommendation of format and content of an sBRA using some example text for paracetamol

Section	Description	Some appropriate text for inclusion in an assessment for paracetamol
Product details	Product details should list all available drug formulations in the marketing authorization. It may consist of the trade name(s), generic name(s), dose, dosage forms, and countries in which the drug is available. It should also include a sub-section listing all approved indications and a subsection on the identified and potential risks, including any possible risks currently under evaluation.	• *Paracetamol has been licensed for use in the EU since the 1970s* • *Approved indications include mild-to-moderate pain, mild-to-moderate fever, and arthritis* • *Identified Risks include hepatotoxicity in case of over-dose* • *Potential Risks include thrombocytopenia/agranulo-cytosis.*
Product overview	The overview should provide a summary, including information on the product's mech-anism of action and regulatory history.	• *Paracetamol is a para-aminophenol derivative with analgesic, antipyretic and anti-inflammatory activity attributed to the inhibition of prostaglandin signaling.*
Benefit evaluation	The product's benefits should be described per indication and include information on the target population, such as the disease's incid-ence or prevalence. It should also specify the strength of the evidence supporting the drug's efficacy for this indication and any missing information about the effectiveness of this indication.	*Benefits for indication 'Arthritis.'* • *Approved by major regulatory authorities (RAs) (1970s)* • *Superior to placebo in 5 of 7 RCTs with a similar safety profile* • *Recommended by major EU/US clinical guide-lines as first-line (alone or in combination with NSAIDs) for hip or knee osteoarthritis.*
Risk evaluation	A full and detailed characterization of each safety concern, and any possible risks under evaluation at the time of preparation of the sBRA, should be provided in the section on risk evaluation.	*New possible risk of severe skin reactions.* • *Results of medical literature review and safety database searches support a potential causal association.*
Benefit-risk analysis evaluation	The benefit-risk analysis evaluation sum-arizes all indications combined using the data presented in the prior sections.	Benefit-risk analysis. • *Benefits for all indications include long-term evidence of efficacy and safety and ready availability to a broad patient population.* • *Risks and possible risks include Hepatotoxicity, Over-dose, SCARs, and exposure during pregnancy.*
BRA discussion	The discussion should summarize the key factors contributing to the product's balance of benefit and risk.	• *Benefit-risk balance seems to remain positive based on the publicly available data.* • *Further analysis of safety data from the marketing authorization holder may be needed to confirm the conclusion.*

DISCUSSION

sBRAs contribute to pharmacovigilance practices across the lifecycle of a product. The BRB can shift over time as new data emerge from greater patient exposure, off-label use, specific age groups, expanded indications, regional clinical practices, new formulations, and new registries, even for well-established products. Concurrent updates to medical terminology should support enhanced clarity and dissemination of clinical knowledge. In pharmacovigilance, the Medical Dictionary for Regulatory Activities (MedDRA), updated twice yearly, is a lexicon that plays an indis-pensable role in providing a common language for health conditions and adverse events (AEs). (35) Proper use of this standardized terminology across pharmacovigilance (PV) activities helps to ensure the compilation of data from diverse sources is comparable.

sBRAs may also help to ensure robust data collection and assessment of some uncertainties and limitations regard-ing the safety profile of a given product. For example, vulnerable or fragile populations such as children, older adults, people with specific underlying conditions, and pregnant women are often underrepresented in the clinical trials used to obtain drug approval (i.e., "pivotal trials"). These populations may have clinically relevant variations in their drug metabolisms pertinent to the patients included in those pivotal trials. As such, the data later collected and assessed for sBRAs over the product's lifetime can ensure that information for these groups of patients is assessed systematically as it becomes available.

Additionally, the evolution of clinical medicine can impact the BRB, as new clinical entities are recognized. A recent example comes from COVID-19, the clinical condition that arises from infection with the newly discovered SARS-CoV-

2 virus. Due to the global pandemic that began in early 2020 and is ongoing at the time of this article's writing, the disease's complete clinical course and complications may not yet be fully recognized or characterized. The evolving clinical features of COVID-19 have been a moving target for drug development and PV. Already approved for use in other conditions and readily available, existing drugs have been the predominant focus of clinical studies in the search for COVID-19 treatments (36). Pharmacovigilance and ongoing sBRAs have played an important role in establishing which existing drugs demonstrate a favorable BRB in the treatment of COVID-19, such as dexamethasone (37,38), and those which did not, such as hydroxychloroquine (39) and ivermectin (40). Based on their mechanism of action, there has been a concern over the theoretical risk for non-steroidal anti-inflammatory drugs (NSAIDs) to exacerbate symptoms of COVID-19, a concern supported by anecdotal and clinical observations. (41) This has raised the possibility of an additional benefit to using paracetamol, rather than NSAIDs, as a part of the treatment for fever and pain in symptomatic COVID-19 patients. We sincerely hope that PV professionals and other readers all around the globe are inspired to continue investigating further the potential expanded utility of Paracetamol and other existing medications in the prevention and treatment of COVID-19.

CONCLUSION

Benefit-risk assessments are essential to the practice of pharmacovigilance. Using an sBRA format helps to ensure that all factors contributing to the overall BRB are considered. Marketing Authorization Holders and HAs may consider the collaborative development of clear and robust sBRA templates and guidelines to further enhance the capabilities of robust PV systems.

ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
AGEP	Acute Generalized Exanthematous Pustulosis
APAP	N-acetyl-p-aminophenol
ASD	Autism Spectrum Disorder
BRA	Benefit-Risk Assessment
BRB	Benefit-Risk Balance
CMDh	Co-Ordination Group for Mutual Recognition and Decentralized Procedures – Human
DILI	Drug Induced Liver Injury
EC	European Commission
EU	European Union
FDA	Food and Drug Administration
HA	Health Authority
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over-the-Counter
PRAC	Pharmacovigilance Risk Assessment Committee
PV	Pharmacovigilance
RA	Regulatory Authority
RCT	Randomized Clinical Trial
sBRA	Structured Benefit-Risk Assessment
SCAR	Severe Cutaneous Adverse Reaction
SJS	Stevens Johnson Syndrome
TEN	Toxic Epidermal Necrolysis
WHO	World Health Organization

CONFLICT OF INTERESTS

The authors declare no conflict of interest regarding the publication of this paper.

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