Prevalence of paracetamol use during early development and the need for interventional safety studies.

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Abstract

Concerns over a causative relationship between paracetamol exposure in the presence of oxidative stress during early development and severe adverse neurlogical outcomes were raised in 2008 and have been fueled subsequently by more than a dozen independent studies. Review of the literature revealed that, although its use is not regurlarly monitored, paracetamol has achieved near universal acceptance, with exposure in some pediatric populations exceeding 90%. In addition, the findings reveal that misuse of paracetamol is common, and that pharmaceutical advertising may played a key role in popularizing the drug. Although retrospective studies might be envisioned to further address this issue, in silico simulations were employed and demonstrated that such studies will be confounded by very high rates of use of the drug combined with associations between paracetamol use and factors associated with oxidative stress. These findings demonstrate that prospective, interventional studies are warranted to evaluate the effects of paracetamol exposure during early development. However, the view that paracetamol is safe is guarded by substantial confirmation bias, consensus bias, and possibly emotional compromise, factors which have undoubtedly led to substantial resistance to any proposed execution of such interventional studies in the past.

Introduction

Paracetamol (acetaminophen) is a widely known anti-pyretic and analgesic, with varied mechanisms of action that affect multiple organ systems. The primary means of anti-pyretic action involves inhibition of cyclooxygenase II, an enzyme necessary for the biosynthesis of prostaglandin E2, a lipid which is in turn necessary for brain development and architecture. Analgesic activity, on the other hand, is achieved through potentiation via the cannabinoid/vanilloid tone in the brain and in the dorsal root ganglia (1, 2).

Paracetamol is biochemically processed and eliminated from the body much like other drugs. The primary means of disposal involves addition of sulfate or glucuronate, which inactivates the drug and facilitates excretion (3). Although some fraction of the drug is usually oxidized, resulting in production of the highly toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI), this toxic metabolite is rapidly inactivated by conjugation with glutathione and secreted under typical conditions. However, under conditions of oxidative stress, more NAPQI is often produced, and removal of the toxic metabolite is profoundly impaired due to depleted glutathione reserves (3). Under these conditions, NAPQI reacts with a wide range of proteins, permanently damaging those proteins and resulting in toxicity to the associated cell. Such toxicity is responsible for life-threatening paracetamol-induced liver injury in thousands of adults per year. Yoon and colleagues, for example, reported that 30,000 patients are admitted yearly for paracetamol hepatotoxicity (4). Further, Agrawal and Khazaeni reported 56,000 emergency room visits, 26,000 hospitalizations, and 500 deaths per year due to paracetamol toxicity (5). Unfortunately, several studies in laboratory animals have demonstrated that paracetamol has profound and long-lasting effects on neurodevelopment at doses vastly lower than lethal doses of the drug (6, 7). Further, numerous studies with varying degrees of control for confounding factors have observed associations between use of paracetamol and neurodevelopmental disorders in humans (8-21). These observations raise a frightening specter for current pediatric practice, in which the amount of paracetamol being used is not systematically tracked and is widely considered to be safe when used as directed, without caveats.

Most studies examining the effects of paracetamol during early development have focused on exposure during pregnancy and have found associated long-term but relatively minor impairments such as delayed speech and learning. However, based on the epidemiology of autism spectrum disorders (ASD), work in animal models, and limited but compelling circumstantial evidence including studies in humans, a causal relationship between paracetamol use during early childhood and the development of ASD appears to be very likely (22). In the working

model describing this causal relationship (22), oxidative stress, which promotes production of NAPQI, the toxic metabolite of paracetamol, acts as a cofactor with paracetamol to induce severe neurological damage during early development (**Figure 1**).

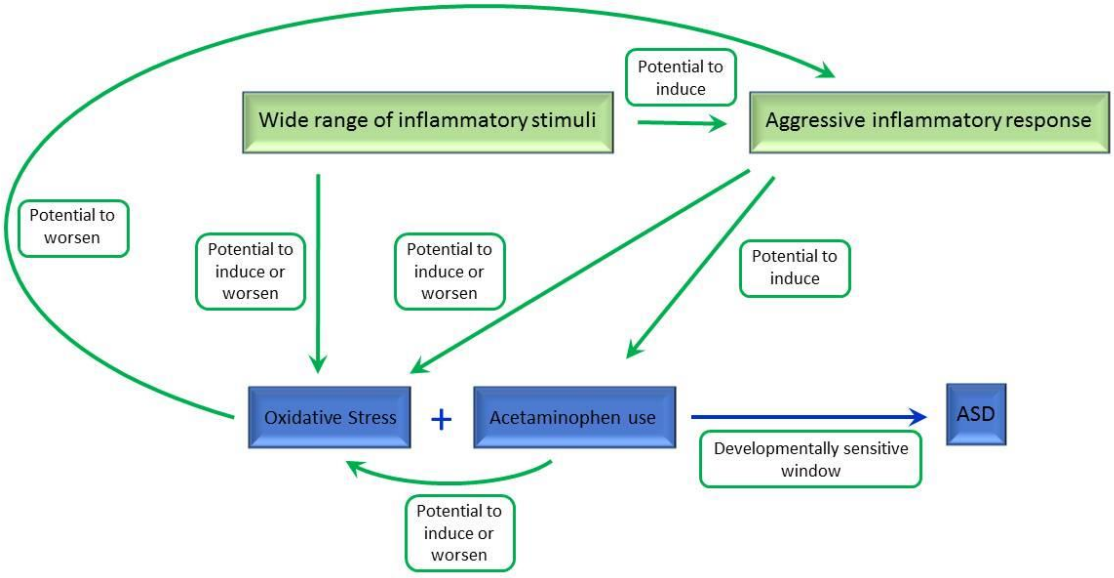

Figure 1. The apparent role of oxidative stress and paracetamol use in the induction of autism spectrum disorder (ASD). In this model, two necessary but insufficient alone factors induce ASD (blue equation). However, multiple connections between the two necessary factors (green sections of diagram) confound classical multivariate analysis.

In this model, paracetamol exposure without oxidative stress is considerably safer: without sufficient oxidative stress, neurodevelopment proceeds in a much more usual fashion despite exposure to the drug. This model is consistent with the wide range of observed risk factors associated with ASD, all of which induce oxidative stress (22). However, this view is agnostic as to whether more subtle neurodevelopmental problems may be associated with paracetamol exposure in the absence of oxidative stress during early development.

In this manuscript, current practices regarding the use of paracetamol are critically reviewed, with special emphasis on the pervasiveness of use and misuse in the pediatric population. Then, based on the very common use

of the drug and its known association with factors such as infection that induce oxidative stress, we use in-silico models to evaluate the ability of retrospective studies to ferret out the contribution of paracetamol use to neurodevelopmental disorders in human populations. Finally, we discuss bias in the field which may impede implementation of the prospective studies needed to examine the neurodevelopmental consequences of early-life exposure to paracetamol.

Methods

Literature search for determination of current prevalence of use of paracetamol in the pediatric population.

Given the widespread assumption that exposure to paracetamol during early development is safe when used as directed, little impetus exists to monitor exposure to the drug, and most studies which do document use of the drug do so coincidentally, as part of another study. Thus, although numerous studies do evaluate childhood exposure to paracetamol, location of such data is better accomplished using the intuition of experienced investigators rather than a systematic search. With this in mind, PubMed databases were searched using a variety of a combination of terms, including the following: paracetamol or acetaminophen, use, dosage, exposure, pregnancy, prenatal, maternal, pediatric, newborn, infant, children, toxicity, overdose, analgesic, antipyretic, fever, survey, and pain.

In silico creation of virtual patient populations.

To evaluate the potential for a multivariate logistic regression analysis of retrospective data to accurately identify the potential contribution of paracetamol use to neurodevelopmental disorders, the following in-silico simulation was performed: A dataset that contained a randomly generated “stress variable” for a population of 12000 virtual subjects was generated using R version 3.6.1. The variable was generated by picking a value from a normal distribution with a mean of 5 and a standard deviation of 2.

Using Microsoft Excel 2016, The 12000 variables obtained using R were shuffled to create an initial data set describing a virtual “cohort” of 12000 individuals such that oxidative stress was described as the sum of 10 variables, each normally distributed and randomly assigned across the virtual “subjects” in the population. Paracetamol use defined as either positive or negative using R, and was set at 97% in the population (3% total with the absence of use). Again using R, paracetamol use was linearly distributed based on total oxidative stress such that those having maximum oxidative stress were assigned to 100% paracetamol use, and those with the least oxidative

stress were assigned to 94% paracetamol use (average of 97% paracetamol use). Finally, using Excel, the prevalence of autism was set to 1% and arbitrarily assigned as those virtual individuals with the highest oxidative stress plus use of paracetamol.

Statistical analyses of resulting virtual data sets were analyzed using SAS (SAS Institute, Inc., Cary, NC).

Results and Discussion

Paracetamol is widely used in the pediatric population, but the extent of use remains unknown

Paracetamol is widely used to control pain from birth to early childhood for a variety of reasons. It is often combined with other pain relief to decrease opioid use, especially for postsurgical pain in newborns (23). In the widely cited consensus statement from the International Evidence-Based Group for Neonatal Pain (24), the authors state "The efficacy and safety of repeated paracetamol doses are unknown", but the drug is nevertheless suggested for "routine NICU care and procedures" as well as for circumcision and heel lancing. Paracetamol is also commonly used for relief of discomfort during teething (25) and vaccination (26), although use during vaccination may impair the effectiveness of the vaccine in some cases (26). Paracetamol is also the most commonly used drug to reduce fevers in the pediatric population.

Several studies have examined the use of paracetamol in the pediatric population (**Table 1**), but no study has accurately assessed the total exposure of any child from birth. For example, using a nationally representative

Study Population	% exposed to paracetamol	Years studied/reference
Infants in England aged 6 months or younger (n=6,973)	84	July 1991-June 1992 (85)
Pregnant mothers in England at 18 weeks of pregnancy, asked about use during last three months (n=8,330)	53	1991-2016 (13)
Pregnant mothers in England at 32 weeks of pregnancy, asked about use during last three months (n=8,050)	42	1991-2016 (13)
Pregnant mothers in New Zealand (n=871)	49.8	1995-1997 (17)
Pregnant women in Denmark (n=1,491)	59	1996-2008 (18)
Pregnant women in Norway (n=51, 200)	40.5	1999-2008 (9)
Children in the US aged 0-10 years at pediatric emergency department, who received either paracetamol or ibuprofen in the past 24 hours (n=200)	70	May-July 1998 (50)

Cases of drug poisoning of children up to 14 years in Spain (n=13,044)	11	1998-2000 (86)
3 year-olds in Norway (exposure in utero) (n=48,631)	46.1	1999-2008 (14)
Pregnant women in Norway (n=112,973)	46.7	1999-2009 (10)
Boys less than 6 years old in the US, exposed to an antipyretic-- cases from the National Poison Data System (n=623,995)	39.8	2000-2015 (87)
Girls less than 6 years old in the US, exposed to an antipyretic --cases from the National Poison Data System (n=564,267)	40.5	2000-2015 (87)
Children in Canada with a fever at an emergency department (n=209)	84.7	Pre-2002 (88)
Children in the United Arab Emirates aged 16 or younger at a pediatric emergency department for fever (n=264)	91.6	March-May 2004 (54)
Children in Spain at age 1 (in-utero exposure up to gestational week 32) (n=2,195)	43	2004– 2007 (20)
Children in the US who did not receive a diagnosis of autism (exposure aged 12-18 months) (n= 68)	75	July 2005- January 2006 (78)
Children in the US aged 12-18 months with a diagnosis of autism (exposure aged 12-18 months) (n= 69)	94	July 2005- January 2006 (78)
Children in Australia aged 6 months-5 years (n= 401)	94	Pre 2007 (53)
Children in Denmark under 10 years of age whose parents reported administration at any time (n=100)	75	April-May 2008 (89)
Children in Denmark under 10 years of age whose parents reported administration within the last three months (n=100)	60	April-May 2008 (89)
Children in Turkey aged between one month and 16 years admitted to a pediatric emergency department with a fever (n=200)	65.5	January-March 2008 (49)
Children in Turkey aged 0-6 years given paracetamol by parents (n= 388)	96.6	March-June 2010 (90)
Children in Turkey aged 0-14 years given paracetamol for fever prior to arrival at the health center (n= 205)	41	April-July 2014 (51)

Children in the US with ASD between the ages 3 to 12 given paracetamol before the age of 2 (n=823)	93.4*	April-May 2017 (12)
Children in the US between ages 3 and 12 before the age of 2 (n= 463)	90.3*	April-May 2017 (12)
Children in the US aged 3, whose mothers reported use of an over-the-counter-medicine in the past 30 days (n= 4,374)	66.7	1991 (27)

Table 1. Percent of individuals given paracetamol. *Percentages exclude cases where it is unknown whether or not a child was administered paracetamol.

sample and weighting, Kogan et al. (1994) estimated that 35.4% of three-year old children in the United States were given paracetamol in the previous 30 days (27). Another study using data from 1999-2006 estimated that 1 in 10 children used a cough and cold medication in a given week; though paracetamol use was not specifically studied, the authors noted that approximately 20% of cough and cold products contained an analgesic, almost always paracetamol (28). Although data that effectively encompass paracetamol use during the entire life of the child are lacking, several studies find very high rates of exposure, in some cases over 95% (Table 1). Notably, a recent NIH-funded examination of the association between neuropsychiatric disorders and the products of paracetamol metabolism in cord blood found that 100% of more than 200 cord blood samples contained paracetamol (11).

Misguided use of paracetamol to treat fevers

Existing studies suggest that paracetamol is not administered to children in a manner that weighs the drug's evident benefits against its risks, resulting in an overaggressive administration of antipyretics in children. This problem involves misconceptions regarding what temperature constitutes a fever, the dangers posed by fevers, and the extent to which antipyretics can prevent adverse clinical outcomes associated with fevers.

By definition first described by Carl R.A. Wunderlich more than a century ago (29) and still widely accepted today (30), a fever in humans constitutes a temperature greater than or equal to 38°C (100.4° F). However, a temperature of 38.3°C (100.9° F) is a more appropriate cutoff for a fever (31), with many healthy infants having a normal temperature of 38.1°C or 38.2 °C, especially during the summer months (32). Nevertheless, approximately half of parents consider a temperature of less than 38°C (100.4°F) to be a fever (33), and among surveyed pediatric

emergency nurses, 46% also stated that a temperature less than 38°C is considered a fever (34). These findings indicate that many parents as well as health care workers do now know how to accurately define a fever.

Fever under a variety of circumstances, including brain injury, is associated with worsened outcomes and can lead to damage to specific organs, including the kidney and the liver (35). However, most fevers, associated with infection, constitute a critical component of the immune response to infection and are beneficial (36, 37). Evans at al. (2015), for example, assert that an increase of 1 to 4°C in core body temperature is associated with "improved survival and resolution of many infections" (38). With this in mind, anti-pyretic treatments are, in fact, immunosuppressive. Further, even within an upper range of 40°C to 42°C, there is no evidence to suggest fevers in children present an increased risk for adverse health outcomes such as brain damage (30, 36, 37).

Several investigators have reported "fever phobia"—exaggerated concerns about fever in children and its complications (seizures, brain damage, etc.) (30, 33, 36, 39, 40). Ninety-one percent of caregivers believe fevers can have harmful effects, with 21% of caregivers listing brain damage and 14% listing death (33). Fever in children causes disproportionate anxiety even health care professionals; for example, among pediatric emergency nurses, 38% state that temperatures less than 40°C could cause serious complications (34). Sixty percent of pediatricians state that temperatures at 104°F (40°C) or greater can cause seizures, brain damage, or death (41).

Consequentially, antipyretics are administered by caretakers (30, 33, 39, 40) and pediatric health care professionals (34, 41), even when there is minimal fever or no fever. A survey of 340 caregivers in two hospital-based pediatric clinics in Maryland found that 25% of caregivers gave antipyretics for temperatures under 37.8°C (less than 100°F) (33). Another survey of 230 caregivers of children in a Pediatric Emergency Department in Virginia reported that 63.9% considered a temperature of less than 37.8°C to be the minimum temperature for antipyretics (39). A survey of caregivers of 201 children in Israel estimated that 65.2% caregivers indicated that they would administer antipyretics for temperatures lower than 38°C (42). Finally, among pediatricians in Massachusetts, 72% reported they always or often recommended treatment to reduce fever (including paracetamol), and 89% stated they did so at temperatures between 38.3°C and 38.9°C (41). Further, an Italian study found that a surprising 74% of all administrations of paracetamol for fever were given to treat fevers less than 38.4 °C. The authors conclude that "preventive action should be taken regarding the use of paracetamol as antipyretic drug in children in order to reduce the fever phobia and self-prescription…" (43). Thus, with the possible exception of a study of 402 parents in

Palestine that found that only 1.5% would give antipyretics for temperatures less than 38° (40), numerous studies point toward a wide-spread fever-phobia, with many parents and even health care workers over-treating fevers.

Unfortunately, the efficacy of antipyretics for managing febrile seizures, morbidity and mortality, and discomfort in febrile illnesses is questionable. Studies have shown that antipyretics were not effective and did not prevent recurrent febrile seizures (36, 44-46). Further, there is insufficient evidence to conclude that antipyretics reduce morbidly or mortality in febrile illness among otherwise healthy individuals, though there may be exceptions for children whose metabolic reserves are marginal from either with chronic health conditions or a critical illness (36, 47). Finally, there is a paucity of research on the extent to which antipyretics alleviate the discomfort of fever and illness (36).

Overdoses of paracetamol in the pediatric population

Paracetamol has a relatively low "therapeutic index"—the difference in the amount required for a therapeutic effect and the amount that is toxic is relatively small. A low therapeutic index, coupled with wide availability and apparently wide use, poses safety concerns with respect to dosing (48). Research indicates that some caregivers administer incorrect doses to children, with some studies demonstrating a supratherapeutic dosage being given (42, 49-52) (**Table 2**) and others suggesting doses at too-frequent intervals (39, 42, 50, 52-55) (**Table 3**). Some authors report that a combination of medications containing paracetamol are being given to children, and that this might be a problem (56).

Study Population	% of children administered an overdose of paracetamol	Years Studied Reference
Children in the US of 0-10 years of age at a pediatric department given a known dose of paracetamol (n=140)	15	May-July 1998 (50)
Children in Turkey aged one month to 16 years admitted with a fever to a pediatric emergency department (n=200)	8.4	January-March 2008 (49)
Children in Saudi Arabia younger than 14 years given paracetamol for suspected or confirmed fever in last 24 hours prior to arrival at an emergency department (n=178)	27	March-August 2008 (52)

Children in Turkey aged 0-14 given paracetamol prior to arrival at a primary health care center (n= 205)	12.1	April-July 2014 (51)
Children in Israel aged 0-60 months reported by parents once arriving at a pediatric emergency department for fever (n=201)	34.8	January-March 2002 (42)

Table 2. Percentage of children administered more than the recommended dose of paracetamol.

Study Population	% of children administered paracetamol too frequently	Years Studied Reference
Children in the US given paracetamol prior to arrival at pediatric clinics (n=268)	14*	June-September 1999 (33)
Children in the US of 0-10 years of age given a known dose of paracetamol prior to arrival at an emergency department (n=140)	4	May-July 1998 (50)
Children in the United Arab Emirates aged 16 years or less given paracetamol orally for fever prior to arrival at a pediatric emergency department (n=85)	27*	March-May 2004 (54)
Children in Australia aged 6 months-5 years given paracetamol by parents (n=368)	3.8*	Pre 2007 (53)
Children in Saudi Arabia younger than 14 years given paracetamol for fever in last 24 hours prior to arrival at an emergency department (n=178)	14	March-August 2008 (52)
Children in the US given paracetamol for fever prior to arrival at a pediatric emergency department (n=230)	8*	May-July 2009 (39)
Children in the Negev District in Israel aged 0-60 months, given paracetamol for fever prior to arrival at a pediatric emergency department (n=201)	21.4*	January-March 2002 (42)

Table 3. Percentage of children administered paracetamol more frequently than the recommended frequency. * Percent of those individuals reported having received paracetamol by their parents/caretakers.

A variety of evidence indicates that overdoses of paracetamol in the pediatric population are common. A study of caregivers to 200 children in Turkey, for example, found that 8.4% of the patients received too high a dose of paracetamol (49). Further, a study of another 200 patients aged 10 years or younger at the pediatric ED at Jacobi Medical Center in New York found that 15% of 124 patients receiving paracetamol were given too high a dose of the antipyretic (50). The authors also noted that a combined 51% of caregivers incorrectly stated that dosage should be based on either age of the child or the height of the fever; caregivers who correctly stated that dosage should be based on their child's weight were significantly less likely to give the wrong dosage (RR 0.71, $P < 0.03$, 95% CI = 0.52-0.97) (50). In another Turkish study, 12.1% parents overdosed with paracetamol (51). A study in Saudi Arabia

estimated that 27% of children aged 14 or younger, who had been given paracetamol for fever prior to coming to the ED, were given a supratherapeutic dose of paracetamol (52). Similar results were found in an Italian study, with 24% of children receiving a primary care visit for fever having received an overdose of paracetamol (43). In one of the most dramatic examples of overdosing, among 201 caregivers surveyed in Israel, 34.8% reported administering higher-than recommended doses of paracetamol (42).

In addition to overdose of paracetamol via administration of too much drug, as described above, studies from around the world point toward all too common administration of a greater number of doses within a given time frame than is recommended. For example, an Australian survey of 401 parents found that 3.8% reported intervals of administration that were too short— medication was administered at intervals shorter than the accepted minimum of 4 hours (53). A similar study conducted in New York found that 4% of caregivers administered paracetamol too frequently (50). Furthermore, a survey in Baltimore found that, among 340 caregivers, 14% gave paracetamol every 3 hours or less (33). In another study, this one in Virginia, 8% of 230 caregivers administered the drug too frequently (39). A Saudi Arabian study found that 14% of caregivers administered paracetamol too frequently (52). Twenty-seven percent of caregivers surveyed in Abu Dhabi, United Arab Emirates, reported giving their child paracetamol more frequently than every 4 hours (54). Among 201 children in Israel, 19.9% were given paracetamol every 1-3 hours if their fever persisted (42). Further, a retrospective study showed that 52% of pediatric patients with hepatotoxicity had received adult preparations of paracetamol (55).

Another possible facet of paracetamol overdose is administering different medications that contain paracetamol. A survey conducted by Princeton Survey Research Associates International in 2013 found that 35 ± 6.7% of the parents amongst the 1003 adults surveyed said it was safe to administer the maximum dosage of Children's Tylenol in combination with Children's Tylenol Plus Multi-Symptom Cold to a child (57). Considering that both the products contain paracetamol, this would lead to a dose of paracetamol that is greater than the amount considered safe for children, leading in turn to potentially serious medical complications such as liver damage (48, 56, 58).

Changing use of paracetamol through time

Although changes in paracetamol use over time have not been tracked in any specific study, available evidence indicates that paracetamol usage has steadily increased since the 1980s. In adults, paracetamol induced

liver toxicity can be used as a proxy for paracetamol use. The potential for paracetamol to induce liver failure was discovered in 1966 (59), but was not listed as a significant cause of liver failure prior to 1980 (4, 60). However, by the late 1990s, paracetamol was the most common cause of liver failure in the United States, United Kingdom, and Denmark (61). Among 265 patients from a two-year period (1994-1996) in the United States, Schiødt et al. found that 20% of liver failures were caused by paracetamol toxicity (61). Larson et al. observed the incidence of liver failure due to paracetamol toxicity rose from 28% of total liver failures in 1998 to 51% in 2003, with approximately half of paracetamol-induced liver failures arising from unintentional overdoses (62). While these data point toward a dramatic increase in paracetamol use in the adult population, evidence of this increase is also seen in the pediatric population for reasons that, at least in part, can be readily identified.

In 1950, aspirin was the most frequently sold painkiller (63). The connection between aspirin and Reye syndrome caused a profound change in pediatric practice, with aspirin use giving way to paracetamol during the early to mid-1980s. (64-67). The near absolute switch to paracetamol for pediatric practice was reflected in a 1984 survey of pediatricians and pharmacists in Columbus, Ohio: 90.6% of pediatricians and 97.8% of pharmacists no longer recommended aspirin to their pediatric patients. Further, 90.6% of pediatricians and 95.6 % of pharmacists then recommended paracetamol for pediatric patients. Changing prescribing and dispensing patterns were evident in sales of children's aspirin and paracetamol products: 93.3% of pharmacies recorded a drop in sales of children's aspirin and an equal rise in sales of pediatric paracetamol products. However, the authors note that observed changes in relative drug sales varied across pharmacies (65).

Notably, the increased use of paracetamol outpaced the decreased use of aspirin, suggesting that factors other than declining use of aspirin were driving greater use of paracetamol. A general increase in consumption of pharmaceuticals, for example, likely drove, at least in part, the increase in paracetamol use in the pediatric population (64). Indeed, given the increase in paracetamol-induced liver damage in adults during this same time period, described above, it seems reasonable to postulate that a factor or factors affecting both the pediatric and adult populations were driving up consumption of the drug by both populations. Thus, the finding that aspirin is associated with Reye syndrome is probably not the only factor contributing to the steadily rising use of paracetamol.

One factor introduced in the 1980s, more so than any other factor, may have facilitated the widespread use of paracetamol observed today: Direct-to-Consumer Pharmaceutical Advertising (DTCPA). In the 1980s, both a political shift favoring pharmaceutical companies and a cultural shift of patient and physician collaboration for the

patients' medicines were underway (68). In 1980 the total spending on DTCPA was $12 million. In 1990, it had increased to $47 million and in 1995, to $340 million— more than a 2,800% increase since 1980. Then, exacerbating the situation, FDA regulations of DTCPA were relaxed beginning in 1997 (with final guidance issued in 1999) and again in 2004, making it easier for companies to advertise on radio and television. Between 1995 AND 1998, budgets for drug advertising to consumers nearly tripled, totaling $1.2 billion. Spending on DTCPA peaked in 2006 and 2007, when DTCPA expenditures were $5.4 and $5.3% billion, respectively, before dropping to $4.4 billion in 2008 due to a financial crisis and recession (68).

The overall impact of advertising is difficult to quantify, but is likely very significant. Both negative and positive emotional advertising are considered compelling and are often used (69-71). In this manner, a drug company can present an image of a fussy, unhappy baby, followed by an image of the drug, and finally an image of a happy, laughing baby. In this manner, the pharmaceutical industry is able to paint a favorable picture of their drug much more effectively than they could if they employed spoken or written language that may be prohibited. Not only is the qualitative nature of the advertising extremely compelling, but the quantity of advertising is substantial. A 2001 study tracked the frequency and length of OTC and prescription drug advertisements on network television appearing in a 504 hour period — OTC and prescription drugs represented 4.8% and 2.3% of all advertisements, respectively, and together accounted for more than 8% of all commercial air time (72). The authors noted that an average television viewer may see more than 100 minutes of DTCPA in a year, compared to the 15 minutes per year the average American spends with their primary care physician. Given their availability, purchase of OTC drugs use may be particularly encouraged by DTCPA since they do not require a doctor's prescription that would include guidance on indications and dosage from physicians.

The battle against the opioid crises has, to some extent, further encouraged the use of paracetamol. Paracetamol is viewed as a useful alternative or adjunct to opioids for acute pain relief in the pediatric population (23, 73) particularly in post-surgical care because of its opioid-sparing effects (23). A significant rise of paracetamol prescriptions after 2012 was observed that corresponded to a more moderate decline of opioid prescription rates during the same time period (74). In response to the rising number of deaths due to opioid overdose (75), the CDC issued guidelines for prescribing opioids for chronic pain in March 2016 that reaffirmed the effectiveness of non-pharmacologic and non-opioid pharmacologic treatments (including paracetamol) for treating pain (76).

Given the above information, it is evident that several factors are driving increasing use of paracetamol in the pediatric population, and that these factors do not take into account the potential harmful effects of paracetamol exposure on neurodevelopment. As paracetamol use has grown unchecked, the prevalence of autism has tragically increased (**Figure 2**). Given the numerous independent factors connecting pediatric paracetamol use with autism and other neurodevelopmental disorders (22), action is needed, and needed urgently.

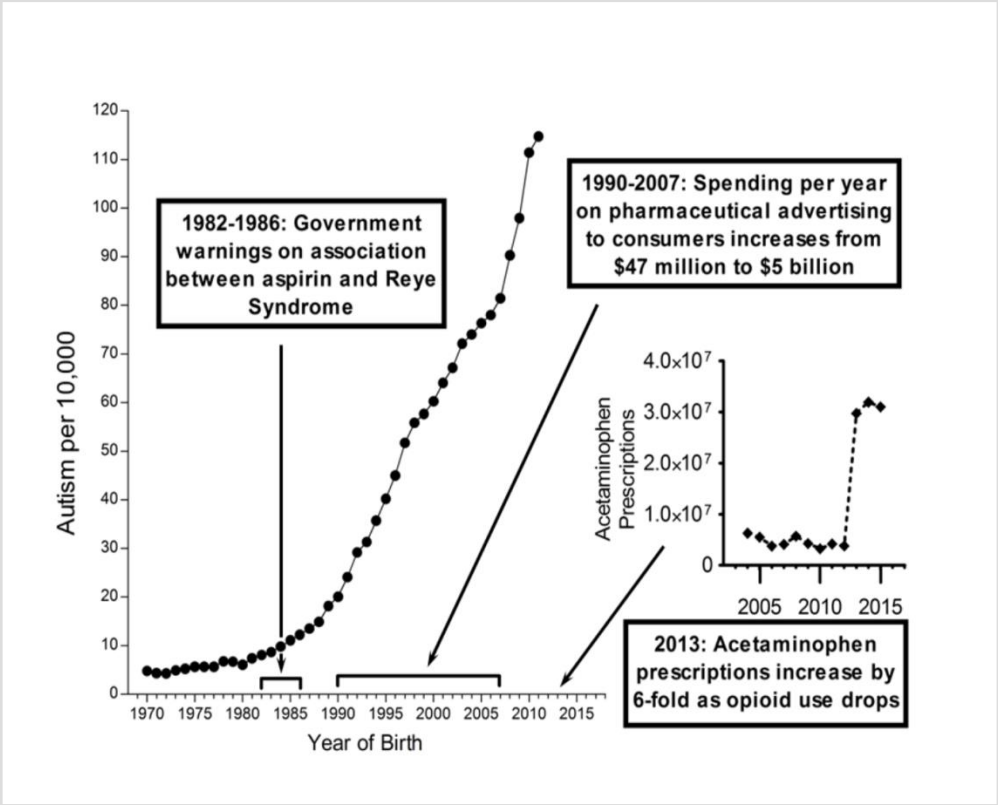

Figure 2. The prevalence of autism in California as compiled by Nevison is shown. Data is a composite of ‘‘snapshot’’ data (information collected at one point in time) from the California Department of Developmental Services (covering birth years 1970–2011) (82). From 1982 to 1986, government warnings on using aspirin due to the association with Reye Syndrome were issued from the Centers for Disease Control and Prevention and the Food and Drug Administration (67). From 1990 to 2007, total spending on direct-to-consumer pharmaceutical adverstising (DTCPA) underwent great increases, going from $47 million dollars in 1990 to $5 billion in 2007 (68). A decrease in opioid use in 2013 (83) accompanied a sudden increase in the number of paracetamol prescriptions as reported by the Medical Expenditure Panel Survey (84).

The need for prospective, interventional studies.

The idea that paracetamol is overused in a manner detrimental to health has been supported by others (77). Of particular concern is the combination of mounting evidence of danger plus the common but misguided view that use and even overuse of paracetamol is essentially risk-free. One approach that might be envisioned to quantify the magnitude of the problem would be a retrospective study assessing the connection between paracetamol use and neurodevelopmental disorders. Indeed, such studies have been conducted, and are consistent with a contribution of paracetamol exposure to neuropsychiatric disorders, even after considering numerous potentially confounding variables (20). This approach, however, is faced with two very significant barriers that may preclude determination of the precise contribution of paracetamol to the problem. First, paracetamol use has reached virtual saturation in the pediatric population, reaching as much as 96 or 97% (Table 1) or even more (11) in some cases. Given this state, paracetamol use can become part of the "background", blinding multivariate analyses to its true influence on disease. Second, the degree of paracetamol use is strongly associated with inflammatory factors such as antibiotic use, ear infections and chronic sinusitis, which are themselves inducers of oxidative stress. Thus, it becomes difficult if not impossible to retrospectively deconvolute the two variables, which is of considerable concern given the working paradigm that both oxidative stress and paracetamol are required to induce neurodevelopmental disorders. Further, since paracetamol is ubiquitous whereas inducers of oxidative stress are varied in the population, we would hypothesize that paracetamol use will "fall out" of a traditional multivariate analysis of retrospective data, even if such use is important for the induction of injury. Fortunately, this hypothesis is readily tested using an in-silico simulation.

To evaluate the potential for a multivariate logistic regression analysis of retrospective data to accurately identify the potential contribution of paracetamol use to neurodevelopmental disorders, a "simple hypothetical population" was artificially created in which the occurrence of autism was strictly induced by paracetamol use in combination with oxidative stress (See Methods). In this hypothetical population, 100% of individuals with autism were exposed to paracetamol, eliminating the possibility of conducting multivariate analysis on the data to evaluate the contribution of paracetamol to the development of autism in the population. With this in mind, adjustments were made to the "simple hypothetical population" to facilitate analysis. First, an additional 5% of all individuals were arbitrarily assigned to no exposure to paracetamol, yielding a data set in which 92% of individuals were exposed to the drug. This created a data set that would mimic, for example, a condition in which paracetamol plus oxidative

stress induced all cases of autism, but 5% of individuals were unaware that exposure to paracetamol had occurred. In a second scenario, the "simple hypothetical population" was modified such that only 50% of the cases of autism were determined by oxidative stress plus the use of paracetamol, whereas the other 50% were randomly assigned. In both of these cases, as shown in **Tables 4 and 5**, exposure to paracetamol but not contributors to oxidative stress dropped far below significance when a multivariate analysis was performed. In other words, the analyses failed to identify paracetamol use as a contributor to the induction of autism, despite the fact that the data set was created using the rule that paracetamol use did, in fact, cause autism when combined with oxidative stress. In a nutshell, the analysis was not designed to identify the contribution of a relatively ubiquitous but important factor that is correlated with other factors that, when combined (to create oxidative stress) are also important.

Obs	Variable*	type3_pvalue	OddsRatioEst	LowerCL	UpperCL	pvalue
1	APAP	0.9582	0.977	0.413	2.311	0.9582
2	VAR1	<.0001	1.767	1.582	1.973	<.0001
3	VAR2	<.0001	1.736	1.559	1.932	<.0001
4	VAR3	<.0001	1.685	1.507	1.885	<.0001
5	VAR4	<.0001	1.635	1.474	1.812	<.0001
6	VAR5	<.0001	1.651	1.482	1.840	<.0001

Table 4: Results of multivariate logistic regression analysis of an artificial data set in which autism was induced by oxidative stress plus exposure to paracetamol, but with 5% of all individuals, regardless of the presence of autism, subsequently assigned to no exposure to paracetamol. * Five out of ten variables contributing to oxidative stress (VAR1 through VAR5) were included in the analysis in order to mimic a realistic data set in which measures of some but not all of the factors contributing to oxidative stress are available. (C-index = 0.75)

Obs	Variable*	type3_pvalue	OddsRatioEst	LowerCL	UpperCL	pvalue
1	APAP	0.7123	1.304	0.318	5.337	0.7123
2	VAR1	<.0001	1.278	1.165	1.401	<.0001
3	VAR2	<.0001	1.278	1.167	1.400	<.0001
4	VAR3	<.0001	1.257	1.146	1.379	<.0001
5	VAR4	<.0001	1.240	1.133	1.357	<.0001
6	VAR5	<.0001	1.287	1.174	1.412	<.0001

Table 5: Results of multivariate logistic regression analysis of an artificial data set in which 50% of autism was induced by oxidative stress plus exposure to paracetamol, and 50% of autism was assigned randomly. * Five out of ten variables contributing to oxidative stress (VAR1 through VAR5) were included in the analysis in order to mimic a realistic data set in which measures of some but not all of the factors contributing to oxidative stress are available. (C-index = 0.75)

This simulation is not intended to demonstrate that retrospective studies are completely blind to the connection between paracetamol exposure and neurodevelopmental disorders. Indeed, retrospective studies have shown that heavy use of paracetamol can be strongly associated with autism even when some confounding factors are considered (12), and our simulations did not factor in levels of use of the drug. However, our study does demonstrate that a retrospective analysis of data and even a prospective, observational (non-interventional) study can be confounded by the association between paracetamol use and oxidative stress factors, and potentially by relatively small errors in reporting of paracetamol use. Pediatric paracetamol use originates from a variety of disparate and difficult to track sources, including administration in the hospital for such common procedures as circumcision and vaccination, and administration of OTC medications by parents and other, often temporary, care providers. Thus, it is highly likely that any retrospective analysis will be fraught with error, regardless of whether paracetamol use is, as in the hypothetical populations described above, a necessary but by itself insufficient component in the induction of autism. This observation points strongly and conclusively toward the need for prospective, interventional studies to probe the role of paracetamol use in the induction of autism.

Bias favoring the safety of pediatric paracetamol use as directed

Although Schultz provided the first evidence that paracetamol may be hazardous to neurodevelopment under certain conditions more than 10 years ago (78), no prospective study has been performed addressing the potential effects of the drug on the pediatric population. Unfortunately, bias on the part of stakeholders that might discourage the conduct of such studies was evident shortly after the Shultz study was published; a rebuttal was soon published by Cox and McDowell arguing that Shultz's work contained "fatal flaws" and should not be used to reconsider clinical practice (79). The rebuttal contained a litany of errors, some of which were pointed out in the published counter-rebuttal by Shultz (80). For example, Cox and McDowell implied that the common use of the drug was an indicator of safety, the classic fallacious argument of *argumentum ad populum*. Other criticisms were nonsensical. For example, Cox and McDowell objected that a sample size should have been calculated prior to the study, despite the fact that the effect size was unknown prior to initiation of the study, and despite the fact that the results were statistically significant. In addition, Cox and McDowell asserted that the study was invalid because parents of children with autism have better recall of the drugs they used than did parents of healthy children. However, no such bias was evident in the data obtained by Shultz, which showed equivalent recall efficiency in both parent groups (78). Further, such bias of recall in favor of parents with sick children is not supported by the literature (81).

In our own experience, we have faced disinterest from administrators in charge of pediatric analgesic safety as well as peer reviews that express unsupported beliefs contradicted by all available data. For examples (with corrections for grammar only): "In fact, paracetamol is the safest drug when used according to guidelines if following medical instructions and doctors' advice." Again, "As the authors state, a "likely causal relationship between paracetamol and autism" is really scary for readers. It is too strong." In the face of such bias, it is vitally important for impartial minds to tenaciously pursue objective testing of the effects of paracetamol on neurodevelopment.

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