



## Research Article

# Trends of acetaminophen overuse among ambulatory patients in Lebanon: an observational study

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### BSTRACT

Acetaminophen (APAP), also known as paracetamol, is used by millions of people worldwide for its antipyretic and analgesic properties. At therapeutic doses, APAP is effective and safe. However, the long-term use and the ingestion of inappropriately high doses pose substantial risks to APAP users. APAP has been the leading cause of acute liver injury across the globe.

No studies previously assessed APAP usage patterns in Lebanon, the objective of the study is to evaluate the appropriateness of APAP use among the community pharmacy patients across Lebanon as a first step to understand and postulate safety recommendation. A cross-sectional survey was performed in 45 pharmacies randomly selected across Lebanon. A 17-item questionnaire was used to record patterns of APAP use among the Lebanese adult population.

2160 participants were found taking APAP or APAP containing products with a mean age of mean  $40.83 \pm 16.36$ . The prevalence of acetaminophen use as single ingredient was 46.8%, while 53.2% were using APAP combination products. One in ten participants ingested a total daily dose of more than the recommended 4 g. Half of APAP users reported taking the drug daily for “as long as they needed it” before consulting a healthcare professional. Heavy alcohol intake was reported by 30.4% of the users and 8% of the users suffered from liver disease.

The study identified APAP over users among a significant percentage of community pharmacy patients in Lebanon. It is essential to raise awareness among patients on the appropriate use of APAP as well as the compelling risks of concomitant chronic ingestion of alcohol and other hepatically metabolized substances.

**Key words:** Acetaminophen, APAP, safety, overuse, community.

## INTRODUCTION

Acetaminophen (APAP), also known as paracetamol, is used by millions of people worldwide for its antipyretic and analgesic properties. At therapeutic doses, APAP is effective and safe. However, the long-term use and the ingestion of inappropriately high doses pose substantial risks to APAP users. Acetaminophen misuse is considered as a real public health threat as it can have several toxic effects including hepatic failure/necrosis and death.<sup>1,2,3</sup> Across the globe, the association between liver injury and acetaminophen use has been thoroughly documented in the literature. APAP was the leading cause of acute liver injury in the US from 1998 to 2003.<sup>4</sup> Results

from a prospective multicenter study revealed 48% (131 of 275) of acute liver failure (ALF) to be associated with accidental APAP overdose.<sup>4</sup> Worldwide, APAP-related ALF is considered the most common etiology of yearly cases of ALF and the most commonly used drug for overdose.<sup>5,6,7</sup> Factors like the availability of APAP as prescription as well as over-the-counter (OTC) formulations, its popularity, the numerous brand names of products containing APAP alone or in combination with other medications, the limited consumers' knowledge in interpreting drug labels, might all lead to the potential harm of exceeding recommended doses. For instance, the Toxic Exposure Surveillance System reported 1,187 poisoning cases that resulted in major injury for OTC single-ingredient products, 653

for OTC combination products, and 1,470 for prescription-opioid combination products.<sup>8</sup>

The various studies on APAP induced ALF lead to a range of regulatory actions at the 2009 Joint Meeting of the FDA Drug Safety and Risk Management Advisory Committee, Nonprescription Drugs Advisory Committee, and Anesthetic and Life Support Drugs Advisory Committee. In attempt to limit the scope of APAP overdose, a boxed warning to prescription APAP products was added, some APAP combination prescription drugs were removed from the market and the amount of APAP in each OTC dosage unit was limited to 325 mg.<sup>9</sup> The challenge of APAP misuse in Lebanon is particularly significant as we lack any data reporting the patterns of APAP use in the community and no national poison control centers or surveillance programs to track APAP overuse exist in the country. Moreover, in Lebanon, all APAP products, whether in the form of tablets, suppository or drinkable solutions are available as OTC and paid for as out-of-pocket. There exist around 55 analgesic formulations, sold in pharmacies, containing APAP as single ingredient with doses of acetaminophen ranging from 125 mg to 665 mg. We also count around 30 products with codeine, caffeine, pseudoephedrine and other ingredients combined to APAP. Analgesics with APAP are easily accessible in pharmacies at very affordable prices starting at half a dollar.<sup>10</sup> In light of this, we performed a drug use evaluation to assess the appropriate use of acetaminophen among the community pharmacy patients across Lebanon as a first step to understand and postulate safety recommendation on APAP use.

## METHODS

A quantitative cross-sectional research design was developed to study the use of APAP among the Lebanese adult population. The study was approved by the Lebanese American University's Institutional Review Board. The purpose of the study was elucidated and participant consent was obtained prior to administering the surveys.

In Lebanon, all drugs including APAP formulations are sold in pharmacies which are easily accessible. Therefore, the targeted population of ambulating Lebanese patients aged 20 years or above, was recruited from a random sample of community pharmacies across different regions of Lebanon over a period of 4 years. To ensure a representative sample of adults, 45 pharmacies were randomly selected across the six Lebanese governorates: North of Lebanon, Mount Lebanon, Beirut, Beirut Suburb, South of Lebanon and Beqaa. In each pharmacy, around 50 subjects were interviewed face-to-face by pharmacy students. Patients of either gender, 20 years of age or greater, were included if using acetaminophen or acetaminophen containing products with or without prescription. Pregnant women and pediatrics were excluded.

### *Instrument*

A 17-item questionnaire was developed based on available relevant literature. The instrument included essential

information on subject's demographic characteristics, type of APAP product(s) used, dose, indication, route and duration of APAP use, presence of concomitant liver disease, and alcohol consumption. Duplication of APAP use was also recorded. To evaluate the clarity of the survey queries, a pilot study was carried out on 18 volunteers. Accordingly, minor modifications were made to question wording and layout based on feedback from the respondents and interviewers.

APAP indication for use, the total daily dose, and the duration of APAP consecutive use before physician's consultation were assessed. The investigators also looked at the proportion of patients using APAP while suffering from liver disease, proportion of patients using acetaminophen while heavily drinking alcohol, proportion of patients using concomitantly more than one medication containing acetaminophen, and classified as "overusers" all individuals taking a daily dose  $\geq 4$  g, or 4 g with the presence of liver disease, or 4 g and ingesting more than 7 alcoholic beverages per week.

### *Data Analysis*

At the end of data collection period, 2160 questionnaires (equivalent to 92% response rate) were filled, coded and entered into the SPSS(version 16, Chicago, USA) and STATA (v. 8) software. The responses were tabulated and cross-tabulated. Mean and standard deviation for the sample age was calculated. Prevalence and 95% confidence intervals (CIs) (using the binomial exact method) of participants using and over-using acetaminophen were computed. Percentages of the pattern of APAP intake were computed to describe the users and over-users. Prevalence of APAP intake by age group among over-users was calculated. Indication for APAP intake among users and over-users was described. Pearson Chi-Square test was used when comparing results. Significance was set at the 5% level.

## RESULTS

### *Patterns of APAP use*

The study sample consisted of 2160 participants taking APAP or APAP containing products with their age ranging between 20 and 90 years (mean  $40.83 \pm 16.36$ ). Demographic information is shown in table 1.

**Table 1: Demographic Percentages**

Age (years)	N= 2160
20 – 29	30.4%
30 - 39	20.8%
40 - 49	19.5%
50 – 59	10.2%
60 – 69	10.6%
70 +	8.5%
<b>Gender</b>	
Male	41.3%
Female	58.7%
<b>Educational level</b>	
No school	1.2%

High school graduate or less	16.8%
Some college	40.7%
University graduate	35.5%
Post-graduate studies	5.8%
<b>Patient-perceived severity of pain</b>	
Mild	24.8%
Moderate	48.3%
Severe	26.9%

The prevalence of exclusive acetaminophen use among the study participants was 46.8% (95% CI: 43.7-49.9%), while 53.2% were using APAP combination products. The most common age group which used acetaminophen was 20-29 years old. Duplication of therapy, defined as the use of 2 or more APAP containing formulation, was noted among 9.1% of the study participants. One in ten participants ingested a total daily dose of more than 4 g. Half of APAP users reported taking the drug daily for "as long as they needed it" before consulting a healthcare professional (HCP), 38% of subjects answered to use APAP for one to seven days before consult and 8.3% of patients reported using it for more than one month before consult. Heavy alcohol intake (defined as more than 7 drinks per week) was reported by 30.4% of the users. Eight per cent of the users suffered from liver disease.

#### Description of APAP over-users

Prevalence of APAP over-users was 15.1% (95% CI: 12.9-17.3%). Among these, 41.7% were using acetaminophen combination products. Two thirds of over-users reported using acetaminophen at a rate exceeding 4g/day. Among over-users, 63.6% ingested daily doses of APAP for as long as they perceived needed without consulting with HCP. Sixty-one per cent admitted drinking more than 7 alcoholic drinks per week and one over-user had a liver disease. Table 2 shows the prevalence of APAP overuse by age groups. APAP intake among over-users was most common among the young age groups, i.e., 21.2% and 19.3% in 20-29 and 30-39 years old respectively. However, the difference in APAP overuse among age groups was not statistically significant according to Pearson Chi-Square test (p-value=0.147).

**Table 2: Prevalence of APAP overuse by age group**

Age (N <sub>total</sub> =326 out of 2160)	APAP overuse % (95% CI)
20-29 (69)	21.2 (14.0-24.6%)
30-39 (63)	19.3 (11.2-22.1%)
40-49 (61)	18.7 (11.1-21.8%)
50-59 (53)	16.3 (8.8-19.7%)
60-69 (47)	14.4 (6.3-18.1%)
70+ (33)	10.1 (1.0-13.5%)

#### Indication for APAP intake

Table 3 shows the medical reasons for APAP intake among users and over-users. Overall, the most commonly reported medical reason for APAP intake among the two groups is "headache". There was no significant difference in the reasons

for taking APAP between overusers and non overusers except for migraine and others (p-value=0.02).

**Table 3: Indication for APAP acetaminophen intake among users and over-users**

Indication	Users % (95% CI)	Overusers % (95% CI)
Headache	42.2 (40.5-46.7%)	45.7 (37.6-53.7%)
Migraine	7.4 (6.5-9.9%)	14.6 (8.9-20.3%)*
Arthritis	5.1 (4.0-6.8%)	4.6 (1.2-8.0%)
Back pain	10.1 (8.8-13.8%)	8.6 (4.1-13.1%)
Dental pain	5.4 (4.2-7.1%)	7.9 (3.6-12.3%)
Menstrual pain	5.6 (6.1-9.5%)	8.6 (4.1-13.1%)
Post-operative pain	3.4 (2.1-4.3%)	3.3 (0.4-6.2%)
Common cold	9.8 (8.6-12.4%)	9.9 (4.8-15.1%)
Others	11 (9.1-14.2%)	5.3 (1.7-8.9%)*

\*P<0.05

## DISCUSSION

Various studies have shown that APAP was the main causative agent of liver failure in the United States and the United Kingdom.<sup>11, 12</sup> Supra-therapeutic doses have been linked to liver injury.<sup>13</sup> Larson et al outlined in their study that liver injury in 48% of patients receiving liver transplants in the United States were caused by unintentional acetaminophen overdose.<sup>4</sup> Such statistics are not available for Lebanon. In our study, we found that fifteen percent of our survey respondents reported ingesting more than the recommended manufacturer's daily dose of 4 grams and were classified as overusers. Several factors can be contributing to the overuse of APAP among our respondents. First, the availability of acetaminophen under two different generic names (as acetaminophen and paracetamol) on the Lebanese market makes it easier for duplication of therapy. Such difference in nomenclature might lead to consumer's confusion and accidental overdose. In addition, the availability of acetaminophen in combination with other products facilitates the ingestion of more than the recommended daily dose. More than 100 products containing acetaminophen were identified on the Lebanese market, all obtainable as OTC. Indeed, 9.1 % of our study over-users reported taking concurrently 2 or more products containing acetaminophen. Patients might have lacked the knowledge that both products contained acetaminophen. It was proven by Stumpf JL, et al that most patients fail to identify acetaminophen as an ingredient in combination products and 7 to 19 % of patients misidentified non-prescription products as containing acetaminophen.<sup>13</sup> Other studies showed that overdosing resulted from apparent overuse of an APAP product or when multiple OTC products were taken simultaneously.<sup>14</sup>

Poor pain management might be another important factor explaining acetaminophen over use. All patients surveyed admitted taking acetaminophen to treat some sort of pain from

headache to post-operative pain. Frustration due to inadequate pain management has been identified in a study as a causative agent for overuse of acetaminophen.<sup>15</sup> The perception of acetaminophen as a safe analgesic in patients as well as HCP might be another factor contributing to acetaminophen overuse.<sup>16</sup>

Lack of patient counseling and instructions and poor physician knowledge regarding acetaminophen dosing and toxicity is also directly linked to overuse of acetaminophen. Hornsby et al showed in their study that many physicians are unaware of acetaminophen dosing and toxicity issues and have some difficulty identifying acetaminophen-containing products.<sup>16</sup>

Thirty percent of our survey respondent admitted drinking alcohol and all identified acetaminophen over-users consumed alcohol. FDA warned that the consumption of 3 or more alcoholic drinks daily while ingesting acetaminophen can increase risk of hepatotoxicity.<sup>17</sup> Moreover, around 8% of our patients took acetaminophen on a regular basis for more than a month without consulting with HCP. The drug leaflet recommends consulting with physician if acetaminophen is to be taken for pain on a regular basis more than 10 days. It is essential to warn patients as well as HCP of appropriate use and duration of APAP intake as well as the compelling risk of alcohol and other hepatically metabolized substances.

### LIMITATIONS

One of our study's limitations is its observational nature. Not all Lebanese pharmacies were included in our sample; however, the big number of patients recruited from different geographical areas as well as the long duration of the study diluted this limitation and made the sample representative. Additionally, patients self-reporting of their APAP use could have been subjective and biased by the recalling ability of respondents. We could not objectively evaluate patients' liver conditions and only collected subjective information on the risk of hepatotoxicity. It would be interesting to examine APAP overdoses and poisoning in emergency departments (EDs) in Lebanon and obtain further clinical data on admitted over-users.

Despite the mentioned limitations, the major strength of our study resides in the fact that it was the first one to report on APAP use across a large number of individuals from across the country.

### CONCLUSION

The study identified acetaminophen over users among a significant percentage of community pharmacy patients in Lebanon. This is a serious finding since APAP over use increases risk of patients developing hepatotoxicity especially if combined with chronic alcohol ingestion. There is a compelling need for spreading public awareness in Lebanon regarding safe APAP use. Healthcare professionals, especially pharmacists, have an integral role in counseling and educating patients on the proper dose of acetaminophen intake, proper label reading and

proper identification of generic and brand APAP names available on the Lebanese market. The government is invited to take regulatory actions to limit the ease-of-access to high dose APAP formulations through national surveillance programs as well as establishment of poison control centers to track and limit medication abuse in Lebanon.

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