

Evaluation of the Annual Sales of Acetylsalicylic Acid, Metamizole and Paracetamol in North Cyprus: Emphasizing the Wide Paracetamol Use

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Abstract

Background: Among the analgesic-antipyretic agents acetylsalicylic acid, metamizole and paracetamol are commonly used. **Objective:** The aim of this study was to analyse the sales of acetylsalicylic acid, metamizole and paracetamol in Northern Cyprus from the pharmaceutical wholesale companies during one year period. **Methods:** We collected the data of annual drug delivery to hospitals and community pharmacy stores between 1st September 2013 and 31st August 2014 from the five most prevalent pharmaceutical wholesale companies that serve in North Cyprus. **Results:** We noticed that oral administration routes of these three molecules were very dominant with 92.88%. Paracetamol was the most preferred with a total annual sale of 117668 boxes (65.25%). 500 mg paracetamol with 65 mg caffeine was the highest among the combined drug formulations of paracetamol (45236 boxes). Metamizole was ranked the second with 18.65%. Drug formulations containing only acetylsalicylic acid were dispensed 24909 boxes, whereas tablets higher than 325 mg were only 5232 boxes. **Conclusions:** Our findings showed that paracetamol was the most preferred analgesic, anti-pyretic agent compared to acetylsalicylic acid and metamizole in North Cyprus. Our results also pointed out that, the use of acetylsalicylic acid for prophylactic purposes like thromboembolic event prevention was higher than analgesic, anti-pyretic and anti-inflammatory purposes.

Keywords: Analgesic, Pain, Paracetamol, Pharmacy Practice

1. Introduction

Pain and fever are two important components of many inflammatory and infectious diseases. Pain is defined by the International Association for the Study of Pain (IASP), as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage¹”. The Centers for Disease Control and Prevention (CDC) considers a person to have a fever when he or she has a measured temperature of at least 100° F (37.8° C) or greater in the “Definition of Symptoms for Reportable Illnesses”².

Acetylsalicylic acid (ASA) is a non-steroidal anti-inflammatory drug with anti-inflammatory, analgesic and antipyretic actions by inhibiting the activity of cyclooxygenase enzyme which leads to the formation of prostaglandins that play role in inflammation, pain and fever³. Prophylactic uses have increased the therapeutic areas of ASA lately. Previous researches have revealed that ASA or ASA including urgent treatments may be able to reduce the risk of recurrent stroke by up to 80% in secondary prevention⁴. Furthermore, research findings determined that the continuous long-term use of low-dose ASA was associated with a 27% reduction in colorectal cancer risk⁵.

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Promising results have also been reported for aspirin-like drugs in Alzheimer's disease and cataract⁶.

Metamizole is used for analgesic and antipyretic purposes. The inhibition of central cyclooxygenase-3 as well as the activations of opioidergic and cannabinoid systems has been proposed as the responsible mechanisms for the analgesic effect. Some hematological system related adverse effects which are the most serious ones may limit its use⁷. Despite this serious adverse effect, a retrospective study which has been performed in a secondary health facility in Nigeria revealed that metamizole was the most commonly prescribed parenteral analgesic drug and owned a 19% portion among all total analgesic drug prescriptions⁸. Another study among Hispanics in Miami revealed that metamizole was used in 28% of the surveyed outpatients in a primary care setting and the most common reasons for using metamizole were pain (72%) and fever (24%)⁹.

Paracetamol is an analgesic and antipyretic agent without an anti-inflammatory action. Although the mechanism of action of paracetamol is not yet fully elucidated, findings focused on that paracetamol revealed his analgesic and antipyretic properties by acting mainly centrally by the inhibition of COX enzymes and peripheral COX inhibition has been discussed recently¹⁰. Additional mechanisms have been proposed like a stimulating effect on descending serotonergic pathways which has been confirmed by in vivo studies¹¹, as well as interactions with spinal 5-HT₃ serotonin receptor subtypes¹², endocannabinoid system¹¹ and spinal Nitric Oxide (NO) formation¹³. Based on a study that has been performed to analyze the use of paracetamol, non-steroidal anti-inflammatory drugs and acetylsalicylic acid in two large United States female cohorts; it has been found that all three classes of analgesics were used frequently. Among younger women, aspirin was the least commonly consumed analgesic whereas it was the most common among older ages. Paracetamol use increased with increasing age. Among 6+ days/week analgesic users, aspirin use was about five-fold higher than paracetamol in women over 52 years-old¹⁴.

According to the aforementioned data, acetylsalicylic acid, metamizole and paracetamol are frequently used worldwide and prescribed for non-specific symptoms, commonly for pain and fever. North Cyprus hosts several international universities and welcomes a high number

of students and tourists every year. This leads to considerable demographical changes during one year period, according to the season as well as the academic calendar. As a result, we aimed to evaluate the use of these three actively consumed molecules to supply a leading data for further detailed researches.

2. Materials and Methods

This study was undertaken to assess the use of acetylsalicylic acid, metamizole and paracetamol including pharmaceutical formulations. For this purpose, we collected the annual drug delivery data from the five most comprehensive and active pharmaceutical wholesale companies that serve in North Cyprus. We have not needed to seek for the ethical approval for the study due to the fact that our research has not included animal or human studies and patient-based specific and private information. However, the required official letters, permissions and the contact information were supplied by Pharmaceutical Directory Office of the Ministry of Health, North Cyprus. The lists of all the pharmaceutical drug formulations are provided from RxMediaPharma[®] 2016, Gemas A.S. Izmir, Turkey. These lists were delivered to the five pharmaceutical wholesale companies that serve to the most of the health facilities in North Cyprus which are Kut[®], Güç[®], Kayra[®], Tane[®] and Sümer[®] companies. They were asked to provide the information about the sales of ASA, metamizole and paracetamol containing pharmaceutical formulations in North Cyprus between 1st September 2013 and 31st August 2014. After gathering of all data from these pharmaceutical wholesale companies, the classifications and calculations of the annual deliveries of ASA, metamizole and paracetamol including formulations were analyzed by the researchers. Data were expressed as total box sales during the mentioned time period. The graphs were obtained by using Graph Pad Prism 6.01 software.

3. Results

Total number of distributed boxes of ASA, paracetamol and metamizole including pharmaceutical preparations in North Cyprus in one year period was 180323 boxes. 92.88% (167488 boxes/year) were oral pharmaceutical preparations. Among the oral dosage forms, the

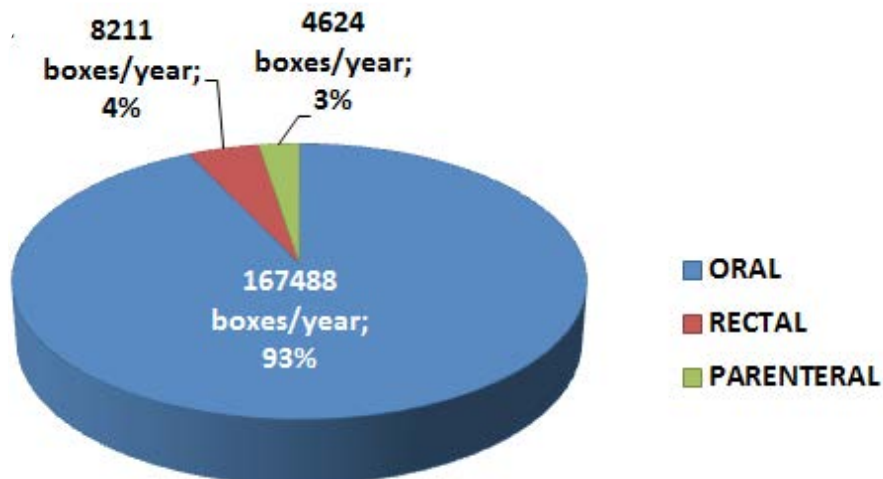


Figure 1. The annual sale of acetylsalicylic acid, paracetamol and metamizole according to their administration routes from the pharmaceutical wholesale companies in North Cyprus (percentage values are rounded).

suspension forms of paracetamol were 9397 bottles/year, whereas metamizole 500 mg, 10 ml drop forms were 22645 bottles/year. Among the administration routes of the three studied drug molecules, 4.55% (8211 boxes/year) was in rectal and 2.56% (4624 boxes/year) was in parenteral forms (Figure 1).

Among the three active ingredients, paracetamol has been found as the highest distributed molecule with a total annual sale of 117668 boxes/year (65.25%). 72432 boxes of paracetamol containing drug formula-

tions was only paracetamol including formulations; however 45236 boxes were the different combination forms of paracetamol with some other active ingredients. Metamizole was ranked second which was followed by ASA; 33625 boxes (18.65%), and 29031 boxes/year (16.10%); respectively. Only ASA including drug formulations were 24909, whereas combination forms with some other active ingredients of ASA was 4122 boxes/year. Metamizole had no combined pharmaceutical formulations with any active ingredients (Figure 2).

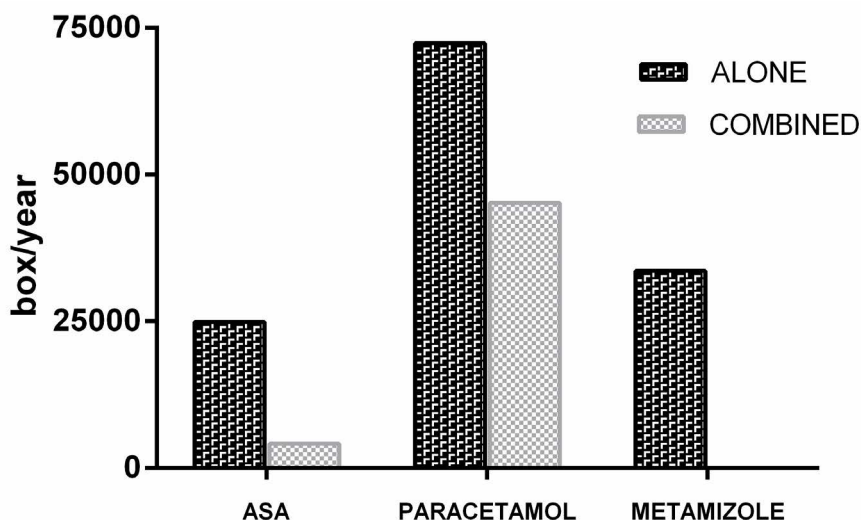


Figure 2. Annual distribution of alone and combined drug formulation forms of Acetylsalicylic Acid (ASA), paracetamol and metamizole in boxes.

Further analysis of ASA drug formulations according to the doses revealed that, only ASA containing formulations higher than 325 mg in one tablet was distributed 5232 boxes/year, however only ASA containing preparations lower than 325 mg in one tablet was 19677 boxes/year (Figure 3). Only ASA containing drug tablets including lower amounts than 325 mg were 80, 100, 300 and 324 mg and annual sales were 480, 2900, 13732 and 2564; respectively. ASA (400mg) combinations with vitamin C (240 mg) was 4072 (Figure 3), ASA (250 mg) combinations with paracetamol (200 mg) and caffeine (50 mg) was 50 boxes/year; respectively. None of the other combinations of ASA which were available in North Cyprus [ASA

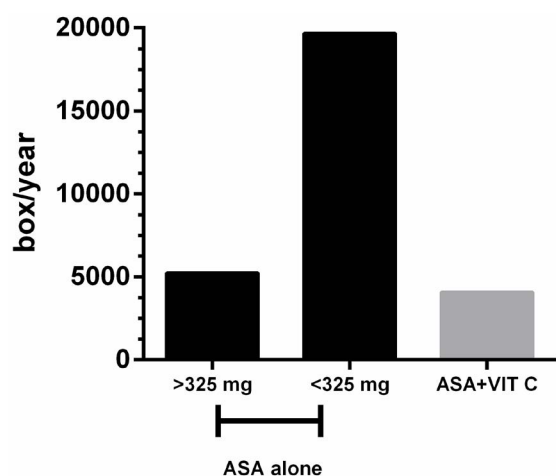


Figure 3. The number of distributed Acetylsalicylic Acid (ASA) drug formulations alone (in doses lower than 325 mg and higher than 325 mg) and in different combination forms.

(300 mg) + Paracetamol (200 mg) + vitamin C (300 mg) and ASA (250 mg) + Paracetamol (200 mg) + Caffeine (65 mg)] were distributed.

Metamizole use in North Cyprus revealed that metamizole was mostly used via oral administration route (97.98%) mainly in 50% drop forms (22,645 boxes/year; 67%) and 500 mg tablet forms 10080 boxes/year; 30%). There were not any combined forms of metamizole available (Figure 4).

Among the 72432 boxes/year of only paracetamol containing pharmaceutical preparations, 9523 boxes were in oral suspension or suppository form, 58965 boxes were 500 mg tablet and 3944 boxes were 10 mg/ml intravenous form. The most preferred combined drug formulation of paracetamol was 500 mg paracetamol + caffeine with 25479 boxes/year (56.32% among all paracetamol-combined drug formulations). 15 mg phenobarbital added to 120 mg paracetamol was distributed 6245 boxes and 200 mg mephenoxalone added to 450 mg paracetamol combinations was 6150 boxes/year. Paracetamol (250 mg) with propyphenazone (150 mg) and caffeine (50 mg) was 2200 boxes and paracetamol (300 mg) with propyphenazone (150 mg) and caffeine (30 mg) was 357 boxes/year. Distribution of ergotamine containing paracetamol preparations were 2,769 boxes/year which is 1969 boxes for paracetamol (325 mg) + ergotamine tartrate (0.75 mg) + caffeine (80 mg) + mecloxamine citrate (20 mg) and 800 boxes for paracetamol (150 mg) + ergotamine tartrate (0.25 mg) + caffeine (60 mg). Additionally paracetamol (125 mg) with adiphenine (25 mg) + allobarbital (30 mg) was 763 boxes/year. Codeine phosphate hemihydrate

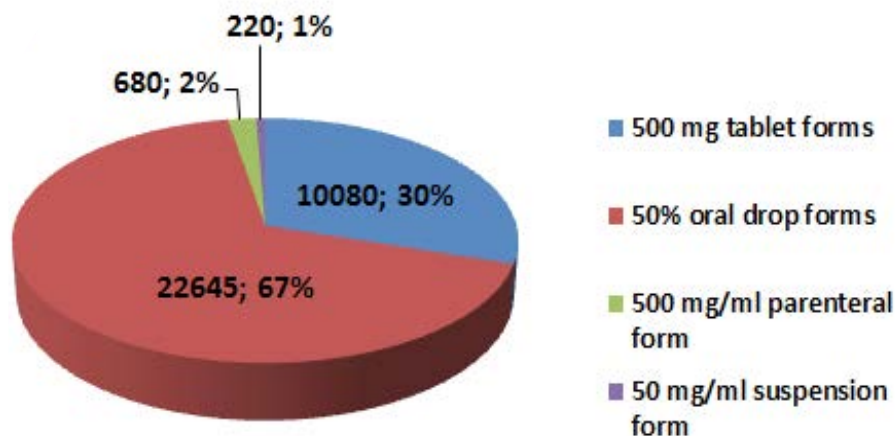


Figure 4. The annual sale of metamizole in oral or parenteral application forms in North Cyprus (percentage values are rounded).

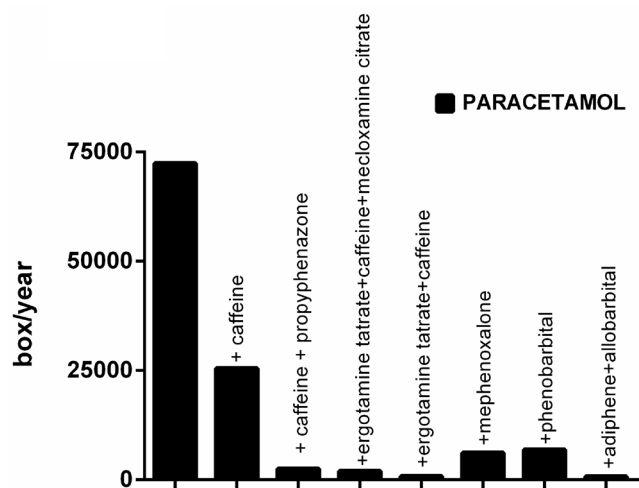


Figure 5. The number of distributed paracetamol including drug formulations (alone and different combination forms).

including paracetamol combinations was 595 boxes and 15 mg phenobarbital with 200 mg paracetamol suppository forms were 638 boxes/year (Figure 5).

Regarding the administration routes, only paracetamol 500 mg containing tablets was the most commonly distributed drug formulation for the oral route which was followed by 50% metamizole drops. Likely to oral route, paracetamol containing formulations was again the most common formulation for parenteral as well as the rectal route (Table 1).

4. Discussion

Aiming to assess the annual distribution of ASA, metamizole and paracetamol, our data revealed that the distribution of paracetamol was 65.25% compared to aspirin and metamizole. Annual use of ASA is less consumed comparison to other agents. According to our knowledge this is the first study comparing the use of three commonly used pain-killers and antipyretic agents

conducted in North Cyprus. One of the limiting factors of our study was the inability to collect the data directly from community pharmacy stores, hospital pharmacies and over-the-counter drug dispensing stores. Related with these limitations we could not expand our study with diagnostic purposes, adverse effects and demographic data. Despite the mentioned limitations, we believe that the results of our study may led to light to design more detailed further studies related with these three commonly used drugs and highlighting that paracetamol use should not be abused due to its adverse effect risks in therapeutic dose ranges.

When the analgesic-antipyretic doses of ASA are considered, this difference becomes more prominent. One possible explanation for this fact may be the relatively higher risk of gastrointestinal system related adverse effects as well as bleeding risks and renal pathologies even in appropriate doses. Another serious risk, related with aspirin use in children in viral infections is Reye's syndrome which is a fatal condition with acute encephalopathy and hepatic injury^{15,16}.

The dose of ASA is an important determinant factor for its therapeutic purposes. The usual adult dose for cardiovascular disease prevention is 75 mg to 325 mg orally once a day¹⁷; whereas it is 325 mg to 650 mg orally every 4 hours as needed for pain management. The dose can be increased up to 6 g per day for anti-inflammatory purposes in arthritis and other rheumatological pain states¹⁸.

In our study, aspirin use over the dose of 325 mg (alone or combined) was 9304 boxes/year whereas paracetamol 500 mg containing tablet distribution was 84524 boxes/year. Controversial to our data, the results of the analgesic use study in Germany showed slightly wider use of aspirin (doses for only analgesic purposes) than paracetamol which was 5.8% for aspirin and 5.2% for paracetamol, in which this difference increased to 5.4% to 2.6% when compared between population over 65 years old¹⁹. Another study in United States revealed an overall increase of 57% from 2005 to 2010 in aspirin

Table 1. The amounts of highest distributions for each active compound according to the administration routes during one year in North Cyprus

	Acetylsalicylic acid (Formulation-boxes)		Paracetamol (Formulation-boxes)		Metamizole (Formulation-boxes)	
ORAL	300 mg tablets	13 732	500 mg tablets	50 744	50% drop	22 645
PARENTERAL	-	-	10 mg/ml	3 944	500 mg/ml	680
RECTAL	-	-	120 mg paracetamol+15 mg phenobarbital	6 245	-	-

use which was 43.6 million adults (19%) reported taking aspirin regularly for at least 3 months. This increase has been attributed to the general idea that regular aspirin use lowers the risk of cardiovascular diseases and may also prevent cancer²⁰. Related with the above information our results showed a considerable difference between the doses of aspirin which is higher than 325 mg (9304 boxes) and lower than 325 mg (80 mg, 100 mg, 300 mg and 324 mg) that accumulated in 300mg tablet form (19677 boxes for < 325 mg, and 13732 boxes for 300 mg tablets). These data can be attributed to the anti-platelet activity and colorectal cancer risk prevention.

In our results among the different combinations of ASA, vitamin C combination was prominent. According to a study on 10 young healthy volunteers, ASA induced significantly more gastric lesions and higher micro-bleeding than ASA-vitamin C combination before and after eradication of *Helicobacter pylori*. The researchers of this study attributed this difference to the attenuation of oxidative stress and pro-inflammatory cytokines with the addition of vitamin C²¹. In North Cyprus, although the cost of ASA-vitamin C was nearly seven-fold higher than single 500 mg ASA tablets, vitamin C combined form distribution was very close to single ASA 500 mg tablet form (ASA 500mg, 20 tablets/box = 0.67 USD/box; Aspirin 400 mg + vitamin C 240 mg, 10 tablets/box = 4.77 USD/box; RxMediaPharma® 2016, Gemas A.S. Izmir, TURKEY).

Our results revealed more common distribution of metamizole than ASA including drug formulations, but lower than paracetamol. Metamizole has been shown to exert analgesic, anti-pyretic and spasmolytic effects. The use of metamizole is still under debate and not admitted in some countries due to its risk for life-threatening adverse events like agranulocytosis and anaphylactic reactions^{22,23}. The limited annual use of metamizole in North Cyprus can be explained by these fatal adverse reactions. Controversially, due to the allergic reactions and increased agranulocytosis risk metamizole prescriptions have been reported to increase four-fold in Germany through 2000 to 2012 keeping its increasing trend for each year²³.

Our results revealed that the distribution of paracetamol was 65.25% compared to aspirin and metamizole. This high rate can be explained by the well-known potential advantages of paracetamol related with patient compliance and drug safety. In therapeutic doses, paracetamol does not irritate the gastric mucosa and safe for coagulation status and kidney functions unlike

aspirin. Reye's syndrome is not a concern in childhood use and availability of oral suspensions and rectal suppository forms enables paracetamol to be used widely in childhood. Paracetamol is a recommended analgesic-antipyretic for pregnant women, new born children and the elderly²⁴⁻²⁶. As the above adverse effects is a concern with aspirin and other non-steroidal anti-inflammatory agents and due to the fact that serious allergic reactions and agranulocytosis should always be considered in metamizole use, paracetamol can be considered as a relatively safer agent when compared with aspirin and metamizole in this aspect. This safety and high tolerability may explain the high distribution rates of paracetamol in North Cyprus.

Despite this common use of paracetamol, some important considerations should not be underestimated. Hepatotoxicity is a serious adverse effect with the overdoses of paracetamol²⁷. However there are accumulating data pointing out the increased liver aminotransferases even in therapeutic doses. 1% of the patients have been reported to have high aminotransferase levels exceeding the upper limit among 9337 patients in a study reviewing the retrospective studies of the paracetamol use in therapeutic doses. Acute liver failure and death have also been recorded in some of those patients²⁸. Additionally some risk factors that have been reported to increase the hepatotoxicity risk should be kept in consideration in paracetamol use like ethanol use¹⁵, concomitant diseases like diabetes mellitus, obesity and myopathies as well as drug interactions especially with some anticonvulsants, rifampin and isoniazid²⁹. As well as liver toxicity risk, asthma, hypotension after anaesthesia and kidney cancer development has been associated with paracetamol use in some researches³⁰. In their recent study, Saengcharoen W et al. emphasized that the insufficient knowledge and tendency to high frequency of analgesic consumption were associated with inappropriate use of analgesics, especially paracetamol³¹. As a result we believe that those mentioned risks for paracetamol should not be overestimated and sufficient knowledge should be given to health care professionals in all points of view as well as to the patients to avoid the paracetamol abuse.

Among the various combined forms of paracetamol, caffeine combinations were the most common. 69% of these combinations were including caffeine alone or with other adjuvant active ingredients. A study assessed the benefit of the overall effect of adding a 130 mg dose of

caffeine to 1000 mg paracetamol in the treatment of mild to moderate pain in a meta-analysis. The outcome of this study showed that the combination of paracetamol with caffeine has significantly greater analgesic activity than paracetamol alone. The benefit of the combination versus paracetamol has been stated as 1.12³². In accordance with the above study, our results showed that 82% of all forms of caffeine + paracetamol combinations were including 65 mg caffeine combined with 500 mg paracetamol meeting with 130:1000 mg ratio.

Our study also revealed that, other active ingredients like barbiturates, muscle-relaxants, opioids, ergotamine and spasmolytic combinations of paracetamol were distributed in North Cyprus. Phenobarbital was the most common among these combinations. This long-acting barbiturate is commonly preferred to be used in the treatment of febrile and non-febrile seizures in both infants and young children³³. Despite this beneficial anticonvulsant effect of phenobarbital, it has been shown that phenobarbital may decrease the cognitive performance in children³³. Besides, in a preclinical model in human hepatocytes the toxicity of paracetamol has been shown to increase with simultaneous administration of phenobarbital³⁴.

5. Conclusion

As a result, our findings have shown that paracetamol is the most preferred analgesic, anti-pyretic agent in North Cyprus compared to ASA and metamizole regarding all administration routes. Only paracetamol containing drug combinations was the most common. Our data revealed a considerable amount of paracetamol + caffeine combination forms. Additionally, the use of ASA for prophylactic purposes like thromboembolic event risk and cancer prevention was higher than analgesic, anti-pyretic and anti-inflammatory purposes. Vitamin C combination with ASA was found close to ASA 500 mg tablets despite the cost. The main reason for the tendency to prefer paracetamol and its combinations in North Cyprus seems to be more likely due to its safety properties related with blood coagulation, GIS adverse effects and safety in pregnancy and children. However, due to accumulating data of some adverse effects associated with paracetamol, this molecule should not be abused and patient related risk factors as well as drug-drug interactions should always be kept in consideration.

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The authors declare that there is no conflict of interest.

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