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REVIEW

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Hair analysis of antidepressants and antipsychotics—Overview of quantitative data

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Abstract

Antidepressant and antipsychotic drugs are regularly encountered in different aspects of forensic toxicology, and some cases require the examination of hair samples. In this study, common antidepressant and antipsychotic drugs regarding hair concentrations over the past decades were reviewed. Although numerous publications around method validations, case reports, or controlled dose studies were found, apparently there is a lack of comprehensive data for many substances. Information on the hair length and dosage across the publications varied largely, and case numbers were generally low except for several retrospective controlled dose studies. Many substances were described only in method validations or case reports, and data were obtained from small case numbers. On the contrary, clozapine, haloperidol, amitriptyline, nortriptyline, risperidone and its metabolite, methylphenidate, citalopram, chlorpromazine, chlorprothixene, and quetiapine had a well-founded database as these substances were investigated in controlled dose studies with higher case numbers. Given the advancements made in analytical techniques over the past years, gas chromatography–mass spectrometry and liquid chromatography with tandem mass spectrometry techniques were the methods of choice and allowed the detection of chemical compounds at low concentrations. The controversy around a potential use of hair analysis to estimate the dosage remains as dose-concentration studies provided divergent results. A harmonization on the investigated hair length as well as on the extraction protocol would be of favor to achieve better comparability. Although hair analysis research focused mainly on drug abuse, availability of more data on antidepressants and antipsychotics would help to gain better knowledge and assist other forensic investigators.

KEYWORDS

antidepressants, antipsychotics, dose-concentration relationship, hair analysispostmortem hair concentration

1 | INTRODUCTION

Hair analysis has become a major technique in forensic toxicology over the past decades and is now routinely used in different applications: drug testing at workplace, examination of driving ability, doping control, diagnosis of drug abuse and chronic intoxication, postmortem toxicology, criminal assaults, therapy compliance control, and the detection of excessive alcohol abuse.[1]

In 2015, Xiang et al[2] published a comprehensive review on drug concentrations in hair and their relevance to drug-facilitated crimes (DFCs). Although this review focused mainly on benzodiazepines, non-benzodiazepine hypnotics, gamma-hydroxybutyrate (GHB), and drugs of abuse, it included the antidepressant amitriptyline and clearly discussed the use of sedating drugs in such crimes. Antidepressants and antipsychotics can be potentially used in DFCs because of their sedating side effects and easy availability by prescription. Many antidepressants and antipsychotics are listed as common DFC drugs by the Drug-Facilitated Crimes Committee of the Society of Forensic Toxicologist[3] and should be a part of general screening methods. Thus, different forensic samples are taken for toxicological examinations. A positive result in a blood or urine sample indicates the exposure to that drug within the past 24–72 h. The complementary analysis of a hair sample is recommended to investigate past long-term exposure to substances. It is important to know the concentration of these substances in hair because hair analysis can help to discriminate between a single exposure and a chronic exposure to a certain degree. This discrimination could be used to support either a victim's claim or an offender's claim, for example, that the offender did not administer any drugs to the victim and that the victim was taking the drug to blame the offender. A segmental analysis is recommended to determine the duration of the exposure in such cases.

Postmortem toxicology sometimes reveals positive findings in blood or urine for drugs not known during the police investigations. A hair analysis can, within its limitations, help to investigate a past use of this drug by the deceased or, in the absence of that, a poisoning by another person with that substance. Hair analysis can also help to investigate a habituation to drugs of abuse. Again, hair concentrations are important to discrimination between a sporadic and chronic intake.

In the emergence of hair analysis, some authors presented controlled studies with correlations between the ingested dose and hair concentration and brought up the idea to use hair analysis for a retrospective therapeutic drug monitoring. The potential use of hair analysis as an alternative matrix in therapeutic drug monitoring was soon after neglected by Tracqui et al[4] who reviewed the available literature and found divergent results for such correlations. The now-well-known aspects of hair analysis lead to inter-individual differences and complicate correlations that are necessary for a retrospective monitoring. However, hair analysis is still a valuable technique for a compliance control if shorter segments are analyzed and significant changes occur in the drug concentration.

Understanding data from hair analysis is key to get to a well-founded interpretation in the mentioned scenarios. All of them can involve antidepressants and antipsychotics because of either their sedative effect[5] or their high prescription rate.[6] These substances are, therefore, regularly encountered in different aspects of forensic toxicology, such as DFCs, postmortem toxicology, or compliance monitoring.

Although Xiang et al,[2] Chèze et al,[7] and Saar et al[8] included some antidepressants and antipsychotics when describing the hair analysis of pharmaceuticals and drugs used in DFCs in their comparative work, there is no comprehensive overview of a large range of substances to our knowledge. This study's aim was to review publications documenting hair concentrations of common antidepressants and antipsychotics and give a comprehensive overview with regard to comparability. Its aim was also to help other forensic investigators with their case work and to improve the interpretation of these drug concentrations in hair analyses.

2 | REVIEW METHOD

The authors did a comprehensive and systematical search on PubMed and Google Scholar databases for English language publications with a focus on concentrations of the most common antidepressants and antipsychotics measured in human hair. Controlled dose studies as well as method validations with an application to authentic hair samples and case reports were included. Combinations of the key words “antidepressant,” “hair,” “LC–MS/MS,” “antipsychotic,” and the respective drug names were used. Numerous drugs have been marketed and classified as antidepressants and antipsychotics over the past decades. The selection of drugs was based on the annual prescription report in Germany[6] and covered the most relevant substances. This relevance might differ in other regions. The selected publications were reviewed for the number of presented cases, investigated hair length, given dosage, and hair drug concentrations. Table 1 summarizes the results for antidepressants and stimulants, whereas Table 2 summarizes the results for antipsychotics. The results are divided into methodology publications, case reports and reports of DFCs, and controlled dose studies with and without the correlation of hair concentration and dosage. In the chapters 3,4 and 5 and for each individual substances in the tables, the publications are arranged in ascending order by year of publication.

3 | METHOD DEVELOPMENT AND VALIDATION PUBLICATIONS

Numerous multi-analyte methods for the simultaneous detection and quantification of selected psychoactive drugs in hair have been published over the past years. Often, besides the description of the validation details, these publications describe the analysis of several drugs as a proof of concept. Hair concentration data from this literature often lack information on the dosage or only involve single or few presented cases.

TABLE 1 Published hair concentrations of antidepressant drugs and stimulants including metabolites

Substance	Concentration range (ng/mg) (n = number of cases)	Dosage	Hair length (proximal segment)	Analytical method	Reference
Tricyclic antidepressants					
Amitriptyline	0.00–17.2 (n = 30)	100–6000 mg (total dose)	3 cm	GC–MS	Tracqui (1992)[9]
	0.04–1.89 (n = 14)	Unknown	Unknown	GC–MS	Kintz (1992)[10]
	3.5–34 (n = 6)	25–50 mg/day	Unknown	GS-MS and HPLC	Couper (1995)[11]
	0.7–106 (n = 7)	Unknown	3 cm	GC–MS	Yegles (1997)[12]
	0.6–11.0 (n = 25)	0.13–2.11 mg/kg daily dose	3 cm	GC–MS	Pragst (1997)[13]
	2.5–57.7 (n = 3)	525 mg per day	2 cm	GC–MS	Shen (2002)[14]
	0.42–3.3 (n = 2)	Unknown	1–3 cm	UHPLC-TOF-MS	Nielsen (2009)[15]
	1.81 (n = 1)	800 mg (poisoning of a newborn baby)	3 cm	LC–MS/MS	Gaillard (2011)[16]
	0.03 (n = 1)	Unknown	Unknown	LC–MS/MS	Lendoiro (2012)[17]
	0.18–1.06 (n = 1)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Chatterton (2013)[18]
	0.037–0.15 (n = 3)	1 case with 25-mg tablet, 2 cases unknown	2 cm	LC–MS/MS	Chèze (2014)[7]
	0.009–0.024 (n = 2)	Unknown (patient under treatment)	9 cm	LC–MS/MS	Fisichella (2014)[19]
	0.007–0.31 (n = 1)	Unknown (repeated administration to a child)	20 cm (1-cm segments)	LC–MS/MS	Chatterton (2014)[20]
	0.054–9.69 (n = 1)	Unknown	4 cm (after acute poisoning) and 5 cm (after 5 weeks)	LC–MS/MS	Allibe (2015)[21]
	0.02–4.8 (n = 2)	Unknown	5 cm and 2 cm (1-cm segments)	LC–MS/MS	Ramírez Fernández (2016)[22]
	0.052–13.6 (n = 24)	180–9000 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]
Nortriptyline	**3.8–9.2 (n = 5)**	25–50 mg/day	Unknown	GS–MS and HPLC	Couper (1995)[11]
	0.05–13.5 (n = 7)	Unknown	3 cm	GC–MS	Yegles (1997)[12]
	0.5–7.9 (n = 25)	0.13–2.11 mg/kg daily dose	3 cm	GC–MS	Pragst (1997)[13]
	1.4–3.2 (n = 2)	Unknown	1–3 cm	UHPLC-TOF-MS	Nielsen (2009)[15]
	0.053 (n = 1)	800 mg (poisoning of a newborn baby)	3 cm	LC–MS/MS	Gaillard (2011)[16]

(Continues)

TABLE 1 (Continued)

Substance	Concentration range (ng/mg) (n = number of cases)	Dosage	Hair length (proximal segment)	Analytical method	Reference
	0.38–2.00 (n = 1)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Chatterton (2013)[18]
	0.007–0.31 (n = 1)	Unknown (repeated administration to a child)	20 cm (1-cm segments)	LC–MS/MS	Chatterton (2014)[20]
	0.057 (n = 1)	Unknown (patient under treatment)	9 cm	LC–MS/MS	Fisichella (2014)[19]
	1.26–8.96 (n = 1)	Unknown	4 cm (after acute poisoning) and 5 cm (after 5 weeks)	LC–MS/MS	Allibe (2015)[21]
	0.03–8.14 (n = 24)	180–9000 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]
Clomipramine	0.37–9.79 (n = 2)	Unknown	Unknown	GC–MS	Kintz (1992)[10]
	0.4–3.9 (n = 7)	0.40–3.44 mg/kg daily dose	3 cm	GC–MS	Pragst (1997)[13]
	1.26–8.96 (n = 1)	Unknown (chronic use)	12 cm (4-cm segments)	LC–MS/MS	Klys (2005)[24]
	0.07–10.7 (n = 3)	120–20 250 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]
N-Desmethyl-clomipramine (metabolite of clomipramine)	0.1–1.5 (n = 7)	0.40–3.44 mg/kg daily dose	3 cm	GC–MS	Pragst (1997)[13]
	4.13–9.71 (n = 1)	Unknown (chronic use)	12 cm (4-cm segments)	LC–MS/MS	Klys (2005)[24]
Doxepin	**7.7–87 (n = 2)**	Unknown	Unknown	GS–MS and HPLC	Couper (1995)[11]
	0.99–3.0 (n = 6)	0.13–0.46 mg/kg daily dose	3 cm	GC–MS	Pragst (1997)[13]
	0.59 (n = 1)	25 mg daily over 4 months	1 cm (5 consecutive samples)	GC–MS	Negrusz (1998)[25]
	55.6–183.3 (n = 5)	100–250 mg per day	2 cm	GC–MS	Shen (2002)[14]
N-Desmethyl-doxepin (metabolite of doxepin)	0.52–2.1 (n = 6)	0.13–0.46 mg/kg daily dose	3 cm	GC–MS	Pragst (1997)[13]
	0.40 (n = 1)	25 mg daily over 4 months	1 cm (5 consecutive samples)	GC–MS	Negrusz (1998)[25]
Tetracyclic antidepressants					
Maprotiline	1.4–40 (n = 13)	0.21–3.07 mg/kg daily dose	3 cm	GC–MS	Pragst (1997)[13]
	3.1 (n = 1)	Unknown	Unknown	LC–MS/MS	Müller (2000)[26]
Mirtazapine	0.38 (n = 1)	Unknown	1–3 cm	UHPLC-TOF-MS	Nielsen (2009)[15]
	0.019–18.9 (n = 3)	Unknown	0.6 cm	LC–MS/MS	Al Jaber (2012)[27]
	0.02 (n = 1)	Unknown (patient under treatment)	9 cm	LC–MS/MS	Fisichella (2014)[19]

(Continues)

TABLE 1 (Continued)

Substance	Concentration range (ng/mg) (n = number of cases)	Dosage	Hair length (proximal segment)	Analytical method	Reference
	8.30 (n = 1)	Unknown	9 cm	LC–MS/MS	Fisichella (2014)[19]
	0.90 (n = 1)	Unknown	0.8 cm	LC–MS/MS	Wang (2018)[28]
Selective serotonin reuptake inhibitors (SSRIs)					
Citalopram	0.25–0.254 (n = 2)	In utero exposure	Unknown	LC–MS/MS	Frison (2008)[29]
	0.07–5.6 (n = 3)	Unknown	1–3 cm	UHPLC-TOF-MS	Nielsen (2009)[15]
	2.5 (n = 1)	Unknown	6 cm (3-cm segments)	GC–MS	Wille (2009)[30]
	0.55–1.10 (n = 1)	Unknown (chronic use)	4 cm (2-cm segments)	LC–MS/MS	Müller (2000)[26]
	5.02– >10.0 (n = 4)	Unknown	Unknown	LC–MS/MS	Lendoiro (2012)[17]
	0.032–2.33 (n = 5)	Unknown (patient under treatment)	9 cm (1 sample segmented in 3-cm segments)	LC–MS/MS	Fisichella (2014)[19]
	2.07 (n = 1)	Unknown	9 cm	LC–MS/MS	Fisichella 2014)[19]
	0.01–132 (n = 8)	10–40 mg	1–16 cm (1-cm segments)	LC–MS/MS	Ramírez Fernández (2016)[22]
	27.1 (n = 1)	Unknown	9 cm (3-cm segments)	LC–MS/MS	Pichini (2016)[31]
	0.15–7.15 (n = 16)	270–3600 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]
	0.001–0.42 (n = 2)	Unknown	3.5 and 4 cm (2-cm segments)	LC–MS/MS	Wang (2018)[28]
	0.12–9.59 (n = 1)	10–30 mg/day	16 cm (1-cm segments and 2-cm segments)	LC-QTOF-MS	Wang (2018)[32]
N-Desmethyl-citalopram (metabolite of citalopram)	0.02–0.12 (n = 2)	In utero exposure	Unknown	LC–MS/MS	Frison (2008)[29]
	0.001–0.18 (n = 4)	Unknown (patient under treatment)	9 cm	LC–MS/MS	Fisichella (2014)[19]
	0.38 (n = 1)	Unknown	9 cm	LC–MS/MS	Fisichella (2014)[19]
	0.13–4.75 (n = 16)	270–3600 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]
Fluoxetine	**4.3 (n = 1)**	Unknown	Unknown	HPLC-DAD and GC–MS	Gaillard (1997)[33]
	1.04 (n = 1)	Unknown	Unknown	HPLC-DAD	Samanidou (2012)[34]
	0.08 (n = 1)	Unknown	Unknown	LC–MS/MS	Lendoiro (2012)[17]
	0.96–1.73 (n = 2)	Unknown	2 cm	LC–MS/MS	Chèze (2014)[7]
	1.12 (n = 1)	Unknown (patient under treatment)	9 cm	LC–MS/MS	Fisichella (2014)[19]

(Continues)

TABLE 1 (Continued)

Substance	Concentration range (ng/mg) (n = number of cases)	Dosage	Hair length (proximal segment)	Analytical method	Reference
	0.75–3.5 (n = 1)	Unknown	9 cm (3-cm segments)	LC–MS/MS	Pichini (2016)[31]
	0.5–8 (n = 2)	Unknown	5 and 6 cm (1-cm segments)	LC–MS/MS	Ramírez Fernández (2016)[22]
	4.85–54.2 (n = 4)	1800–5400 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]
	2.0 (n = 1)	Unknown	2 cm	LC–MS/MS	Wang (2018)[28]
Paroxetine	0.25 (n = 1)	Unknown	Unknown	LC–MS/MS	Smyth (2006)[35]
	0.22–18 (n = 2)	Unknown	1–3 cm	UHPLC-TOF-MS	Nielsen (2009)[15]
	0.09–0.16 (n = 2)	Unknown	Unknown	LC–MS/MS	Lendoiro (2012)[17]
	20.4 (n = 1)	Unknown	2 cm	LC–MS/MS	Chèze (2014)[7]
	2.2–9.5 (n = 1)	Unknown	9 cm (3-cm segments)	LC–MS/MS	Pichini (2016)[31]
	0.02–1.0 (n = 1)	Unknown	16 cm (1-cm segments)	LC–MS/MS	Ramírez Fernández (2016)[22]
	0.71–5.85 (n = 4)	900–1800 mg (total dose)	3 cm	LC–MS/MS	Licata 2016[23]
	0.0006 (n = 1)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Wang (2017)[36]
	11.4–13.8 (n = 1)	20 mg/day	4 cm (2-cm segments)	LC–MS/MS	Wang (2019)[37]
Sertraline	1.9 (n = 1)	Unknown	Unknown	LC–MS/MS	Smyth (2006)[35]
	0.6–2.6 (n = 1)	Unknown	5.5 cm (2-cm segments)	GC–MS	Wille (2009)[30]
	6.54–29.8 (n = 1)	75 mg/day	6 cm (1.5-cm segments)	LC–MS/MS	Papaseit (2012)[38]
	0.12–0.53 (n = 2)	Unknown (patient under treatment)	9 cm	LC–MS/MS	Fisichella (2014)[19]
	0.05–0.1 (n = 2)	50 mg	6 and 8 cm (1-cm segments)	LC–MS/MS	Ramírez Fernández (2016)[22]
	0.43–55.9 (n = 4)	750–9000 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]
	15.1–35.4 (n = 1)	Unknown	9 cm (3-cm segments)	LC–MS/MS	Pichini (2016)[31]
	1.88–4.28 (n = 1)	Unknown	12 cm (2-cm segments)	LC–MS/MS	Marchei (2016)[39]
	0.025–0.5 (n = 5)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Wang (2017)[36]
	0.9–3.63 (n = 1)	25–50 mg/day	16 cm (1-cm segments and 2-cm segments)	LC-QTOF-MS	Wang (2018)[32]

(Continues)

TABLE 1 (Continued)

Substance	Concentration range (ng/mg) (n = number of cases)	Dosage	Hair length (proximal segment)	Analytical method	Reference
	5.2 (n = 1)	Unknown	0.8 cm	LC–MS/MS	Wang (2018)[28]
	14.3 (n = 1)	50 mg/day	2 cm	LC–MS/MS	Wang (2019)[37]
Other antidepressants and stimulants					
Venlafaxine	10–12 (n = 2)	In utero exposure	Unknown	LC-HRMS	Favretto (2010)[40]
	0.035 (n = 1)	Unknown	9 cm	LC–MS/MS	Fisichella (2014)[19]
	0.46–5.81 (n = 6)	3375–20 250 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]
	0.006–0.25 (n = 5)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Wang (2017)[36]
	3.5–14 (n = 1)	Unknown	5.5 cm (1.5-cm segments)	LC–MS/MS	Wang (2018)[28]
Bupropion	0.05–0.6 (n = 4)	150–300 mg	1–4 cm (1-cm segments)	LC–MS/MS	Ramírez Fernández (2016)[22]
Methylphenidate	0.073–1.1 (n = 17)	10–60 mg/day	1–11 cm	GC–MS	Sticht (2007)[41]
	0.15–4.17 (n = 11)	5–36 mg/day	3-cm segments (up to 9 cm)	LC–MS/MS	Marchei (2008)[42]
	0.045–0.15 (n = 1)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Wang (2018)[28]
	0.001–0.26 (n = 10)	Unknown	12 cm (3-cm segments)	LC–MS/MS	Jang (2019)[43]
Ritalinic acid	0.001–0.07 (n = 10)	Unknown	12 cm (3-cm segments)	LC–MS/MS	Jang (2019)[43]
Trazodone	0.01–5.3 (n = 4)	50 mg	1–16 cm (1-cm segments)	LC–MS/MS	Ramírez Fernández (2016)[22]
	6.37 (n = 1)	9000 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]
Duloxetine	0.11–27.4 (n = 16)	1200–5400 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]

Note: Data from postmortem cases are marked in bold letters.

In 1992, Kintz et al[10] presented the results of hair analysis using gas chromatography–mass spectrometry (GC–MS) from a 2-year-period in their institute. The results included data on hair concentrations of amitriptyline, clomipramine, and other drugs of abuse. No information was given on the background of the samples, the analyzed hair length, or dosage.

In 1997, Yegles et al[12] analyzed 21 postmortem hair samples using a GC–MS method after an intake of psychotropic substances was confirmed by toxicological analysis of the blood samples. They focused on the detection of benzodiazepines in a 3-cm hair sample but also included the analysis of amitriptyline in hair. Quantitative results of amitriptyline in hair for seven postmortem cases did not provide any information on the dosage.

Gaillard et al[33] reported the screening, identification, and quantification of drugs in human hair using high-performance liquid chromatography–diode array detection (HPLC-DAD) and GC–MS. The validated methods were applied to five postmortem cases, and data on fluoxetine, promethazine, and other drugs were presented by the authors. The respective hair length or dosage was not known in the cases.

McClean et al[45] focused on the electrospray mass spectrometric fragmentation pattern of antipsychotics and detection of these

TABLE 2 Published hair concentrations of antipsychotic drugs including metabolites

Substance	Concentration range (ng/mg) (n = number of cases)	Dosage	Hair length (proximal segment)	Analytical method	Reference
Typical neuroleptics					
Chlorprothixene	30 (n = 1)	50 mg per day	2 cm	GC–MS	Shen (2002)[14]
	1.1 (n = 1)	Unknown	1–3 cm	UHPLC-TOF-MS	Nielsen (2009)[15]
	0.38 (mean) (n = 20)	28 mg/day - 417 mg/day (estimated)	3–6 cm (1-cm segment)	LC–MS/MS	Günther (2018)[44]
	0.006 (n = 1)	Unknown	2 cm	LC–MS/MS	Wang (2018)[28]
Flupentixol	0.22 (n = 1)	Unknown	Unknown	LC–MS/MS	McClean (2000)[45]
	0.011–0.046 (n = 1)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Wang (2017)[36]
Haloperidol	2.33–245 (n = 40)	3–30 mg/day	1–2 cm (10 samples segmented)	RIA	Uematso (1989)[46]
	3.44–208.1 (n = 59)	3–30 mg/day	1–2 cm (5 samples segmented)	HPLC with coulometry	Matsuno (1990)[47]
	17–242 (n = 2)	5–30 mg/day	Unknown	GS-MS and HPLC	Couper (1995)[11]
	12.2 (n = 1)	150 mg/3 weeks	1–2 cm	LC–MS/MS	Weinmann (2002)[48]
	20.1 (n = 1)	28 mg per day	2 cm	GC–MS	Shen (2002)[14]
	3.23 (n = 1)	Unknown	9 cm	LC–MS/MS	Fisichella 2014)[19]
	4.05 (n = 1)	Unknown	2 cm	LC–MS/MS	Chèze (2014)[7]
	9.3–14.6 (n = 1)	12 mg/day	4 cm (2-cm segments)	LC–MS/MS	Wang (2019)[37]
Promethazine	**5.7 (n = 1)**	Unknown	Unknown	HPLC-DAD and GC–MS	Gaillard (1997)[33]
	0.0002–0.0006 (n = 1)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Kintz (2008)[49]
	0.08–2 (n = 3)	Unknown	1–3 cm	UHPLC-TOF-MS	Nielsen (2009)[15]
	0.0009–0.5 (n = 6)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Wang (2017)[36]
	0.015 (n = 1)	Unknown	5.5 cm (2-cm segments)	LC–MS/MS	Wang (2018)[28]
	0.098–1.9 (n = 4)	Unknown	1.5 cm	UHPLC-QTOF-MS	Kronstrand (2018)[50]
Levomepromazine	**0.08 (n = 1)**	Unknown	1–3 cm	UHPLC-TOF-MS	Nielsen (2009)[15]
	0.001–0.002 (n = 1)	Unknown	8 cm (1.5-cm segments)	LC–MS/MS	Ricard (2012)[51]
	0.66 (n = 1)	Unknown	2 cm	LC–MS/MS	Chèze (2014)[7]
	1.03 (n = 1)	2250.0 mg (total dose)	3 cm	LC–MS/MS	Licata (2016)[23]

(Continues)

TABLE 2 (Continued)

Substance	Concentration range (ng/mg) (n = number of cases)	Dosage	Hair length (proximal segment)	Analytical method	Reference
	0.003–0.25 (n = 4)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Wang (2017)[36]
Sulpiride	0.88 (n = 1)	Unknown	0.6 cm	LC–MS/MS	Al Jaber (2012)[27]
	> 0.25 (n = 1)	Unknown	6 cm (2-cm segments)	LC–MS/MS	Wang (2017)[36]
	19.5–125 (n = 2)	200–600 mg/day	2 cm	LC–MS/MS	Wang (2019)[37]
Pipamperone	**0.9–1.0 (n = 1)**	Unknown	4 cm (2-cm segments)	LC–MS/MS	Müller (2000)[26]
Chlorpromazine	1.6–27.5 (n = 23)	30–300 mg/daily	1 cm (5 samples segmented)	HPLC with coulometry	Sato (1993)[52]
	1.3–29 (n = 2)	Unknown	Unknown	GS-MS and HPLC	Couper (1995)[11]
	1.24 (n = 1)	Unknown	Unknown	LC–MS/MS	McClean (2000)[45]
	2.9–68.2 (n = 16)	100–500 mg per day	2 cm	GC–MS	Shen (2002)[14]
	0.4–7.3 (n = 14)	50–450 mg/day	4 cm (2-cm segments)	LC–MS/MS	Wang (2019)[37]
Atypical neuroleptics					
Amisulpride	**0.0005–0.031 (n = 5)**	Unknown	6 cm (2-cm segments)	LC–MS/MS	Wang (2017)[36]
	9.2–20.3 (n = 2)	200–400 mg/day	4 cm (2-cm segments)	LC–MS/MS	Wang (2019)[37]
Clozapine	0.17–34.2 (n = 23)	200–700 mg/day	3 cm	GC–MS	Cirimele (2000)[53]
	0.47–0.92 (n = 3)	150–400 mg/day	1–2 cm	LC–MS/MS	Weinmann (2002)[48]
	16.7–59.2 (n = 16)	100–500 mg per day	2 cm	GC–MS	Shen (2002)[14]
	0.78–3.38 (n = 12)	8.3–62.5 mg/day	2–7 cm	LC–MS/MS	Kronstrand (2007)[54]
	6.1–60.1 (n = 27)	50–375 mg/day	6 cm (2-cm segments)	LC–MS/MS	Wang (2019)[37]
Olanzapine	0.035 (n = 1)	Unknown (patient under treatment)	9 cm	LC–MS/MS	Fisichella (2014)[19]
	<LOQ–1.44 (n = 5)	10–20 mg/day	6 cm (2-cm segments)	LC–MS/MS	Wang (2019)[37]
Quetiapine	**1.5 (n = 1)**	Unknown	1–3 cm	UHPLC-TOF-MS	Nielsen (2009)[15]
	4.28 (n = 1)	Unknown	9 cm	LC–MS/MS	Fisichella (2014)[19]
	2.60 (n = 1)	Unknown (patient under treatment)	9 cm	LC–MS/MS	Fisichella (2014)[19]
	0.35–10.21 (n = 10)	200–1200 mg/daily	2–12 cm (2-cm segments)	LC–MS/MS	Binz (2014)[55]
	0.10–2.29 (n = 1)	Unknown	12 cm (2-cm segments)	LC–MS/MS	Marchei (2016)[39]
	0.49–2.18 (n = 2)		3 cm	LC–MS/MS	

(Continues)

TABLE 2 (Continued)

Substance	Concentration range (ng/mg) (n = number of cases)	Dosage	Hair length (proximal segment)	Analytical method	Reference
		562.5–4500.0 (total dose)			Licata (2016)[23]
	0.01–3.8 (n = 3)	Unknown	0.8– 7 cm (segmented)	LC–MS/MS	Wang (2018)[28]
	0.18–13 (n = 22)	45 mg/day - 1040 mg/day (estimated)	2–6 cm (1-cm segments)	LC–MS/MS	Günther (2018)[56]
Risperidone	0.036–4.75 (n = 3)	2–6 mg/day	4–18 cm (segmented)	LC–MS/MS	Schneider (2009)[57]
	0.27–0.69 (n = 2)	1–10 mg/day	3 and 6 cm (1.5-cm segments)	LC–MS/MS	Papaseit (2012)[38]
	3.50–28.3 (n = 34)	2.5–5 mg/day	1 cm	LC–MS/MS	Sun (2019)[58]
	2.5–20.2 (n = 12)	2–6 mg/day mg/day	6 cm (2-cm segments)	LC–MS/MS	Wang (2019)[37]
9-OH-risperidone	0.014–0.057 (n = 3)	2–6 mg/day	4–18 cm (segmented)	LC–MS/MS	Schneider (2009)[57]
	0.067–1.24 (n = 34)	2.5–5 mg/day	1 cm	LC–MS/MS	Sun (2019)[58]
	0.04–0.35 (n = 12)	2–6 mg/day mg/day	6 cm (2-cm segments)	LC–MS/MS	Wang (2019)[37]
Aripiprazole	250–730 (n = 9)	10–30 mg/day	4 cm (2-cm segments)	LC–MS/MS	Wang (2019)[37]

Note: Data from postmortem cases are marked in bold letters.

substances in hair. The liquid chromatography with tandem mass spectrometry (LC–MS/MS) method was applied to the hair sample of a patient under treatment with flupentixol, chlorpromazine, and trifluoperazine. No information was available on the regular intake of the substances or the used hair length.

In 2000, Müller et al[26] presented data for the identification of selected pharmaceuticals using the emerging LC/ESI-CID/MS and LC–MS/MS techniques. They focused on the identification of maprotiline, citalopram, and pipamperone in three selected cases (two suicide cases and one patient under treatment with citalopram for 4 months) using extracted ion chromatograms and mass spectra library entries. For the citalopram and pipamperone cases, a 4-cm-long hair (2-cm segments) was analyzed. The used hair length for the maprotiline case was unclear. No information was available on the dosage for all three cases.

Smyth et al[35] characterized the structures and product ions of several antidepressants using an ESI-Ion-Trap and liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) measurements as well as using an LC–MS/MS system. Hair concentrations of sertraline and paroxetine were presented although this publication was mainly about the fragmentation patterns of the selected analytes. In this publication also no information was available on the used hair length or a dosage.

Data on hair concentrations of 15 autopsy cases were presented by Nielsen et al[15] who developed and validated a ultra-high performance liquid chromatography- time-of-flight mass spectrometry (UHPLC-TOF-MS) method for the detection of 52 pharmaceuticals and drugs of abuse in hair in 2009. The dosage was not known in any of the cases, but information was available on the toxicological results from the respective blood samples. About 1–3 cm of hair was analyzed giving data for amitriptyline, nortriptyline, mirtazapine, citalopram, paroxetine, chlorprothixene, promethazine, and quetiapine.

Wille et al[30] described and validated a GC–MS method for the detection of 12 antidepressants and their metabolites in blood, brain tissue, and hair samples. The application of this method to four postmortem cases generated data on hair concentrations of citalopram, fluoxetine, trazodone, and sertraline, including their metabolites. Hair samples of 6 cm (in 3-cm segments) were analyzed, but the dosage was unclear.

Al Jaber et al[27] focused on extraction procedures and compared two extractions for an LC–MS/MS method for the detection of 20 analytes in hair. The application of the method to nine hair samples from patients and one hair sample from an autopsy case revealed a better extraction with methanol and delivered data on hair concentrations of sulpiride, quetiapine, mirtazapine, risperidone, and its metabolite paliperidone. Segments of approximately 0.6 cm of hair were analyzed, while the dosage remained unclear.

Lendoiro et al[17] reported the validation of a target screening of 35 psychoactive drugs in hair using LC–MS/MS and its application to 17 forensic cases as a proof of the applicability of the method. One of the cases was a medical case with a requested drug monitoring, whereas the other cases came from patients after a withdrawal treatment for at least 2 months before sampling. No information was

available on the analyzed hair length or prescribed dosage. Hair concentrations of antidepressants included citalopram, amitriptyline, fluoxetine, and paroxetine.

Samanidou et al[34] presented a HPCL-DAD method for the detection of venlafaxine, duloxetine, fluoxetine, and paroxetine in hair, nail clippings, and cerebrospinal fluid. After validation, the method was applied to the hair and nail samples of a patient undergoing fluoxetine therapy. However, no information was available on the dosage or the analyzed hair length.

Pichini et al[31] developed and validated a method for the detection of 22 antidepressants and anxiolytics in maternal hair and neonatal meconium. They analyzed three consecutive maternal hair segments of 3 cm to represent pregnancy trimesters and paired the results with the samples of neonatal meconium. The results from nine mothers generated data on hair concentrations of citalopram, paroxetine, and fluoxetine.

In 2014, Fisichella et al[19] developed and validated an LC–MS/MS method for the detection of 87 psychoactive substances. They analyzed 9-cm-long hair samples from nine patients under pharmacological treatment and hair samples from four autopsy cases. In one case, the hair sample was segmented. Hair concentrations of amitriptyline, nortriptyline, mirtazapine, citalopram, *n*-desmethylcitalopram, haloperidol, sertraline, venlafaxine, fluoxetine, quetipaine, and olanzapine were presented, but the dosage was not known for any of the cases.

Ramírez Fernández[22] presented the validation of an LC–MS/MS method for the detection of 24 antidepressants in hair and then applied it to 18 authentic hair samples for workplace drug testing. The samples had varying hair lengths but were sectioned in 1-cm segments. Concentrations of citalopram, trazodone, sertraline, paroxetine, bupropion, fluoxetine, and amitriptyline and their metabolites in hair were determined. Information about the daily dose was known from self-reports in some cases.

Wang et al[36] developed and validated a targeted UHPLC–MS/MS method for 116 analytes in hair and applied it to 25 postmortem cases with unknown dosage. Hair concentrations from three 2-cm segments were determined for paroxetine, flupentixol, and sulpiride, whereas there were data for levomepromazine, venlafaxine, sertraline, amisulpride, and promethazine from up to five cases.

Another UHPLC-TOF method for the detection of psychoactive substances was validated by Kronstrand et al[50] and applied to 29 autopsy cases. In each case, a 1.5-cm segment was analyzed, but no data were available on dosage. Besides data on several drugs of abuse they presented hair concentrations of promethazine from four cases.

Both Jang et al[43] and Marchei et al[42] presented successful method validations for the detection of methylphenidate in hair using LC–MS/MS. Jang et al[43] applied the method to hair samples from 10 drug users with illegal methylphenidate use, whereas Marchei et al[42] investigated the hair samples of 11 children under known dosage regimen for methylphenidate for at least 6 months. The hair samples were analyzed in 3-cm segments in both studies.

4 | CASE REPORTS AND REPORTS OF DRUG-FACILITATED CRIMES

The primary focus of the presented publications was casework and not the proof of application of a multi-analyte detection method. Reports about DFCs with the use of antidepressants and antipsychotics were also included. Some publications also involved the segmental analysis for a time-resolved investigation.

Klys et al[24] presented toxicological investigations on a fatal clomipramine intoxication of a chronic alcoholic patient who received clomipramine for 1 year before his death. An analysis of the blood sample revealed a possible fatal clomipramine concentration and a high blood alcohol level. The segmented analysis of a 12-cm hair strand (4-cm segments) using LC–MS/MS confirmed the chronic use of clomipramine, whereas the analysis of the direct alcohol marker ethylglucuronide confirmed a chronic excessive alcohol consumption.

Favretto et al[40] and Frison et al[29] presented two publications on the analysis of neonatal hair using LC–MS/MS and liquid chromatography-high resolution mass spectrometry (LC-HRMS), respectively to proof in utero exposure. In the first publication[29] the authors found citalopram in the hair of newborns, whereas venlafaxine and other metabolites were found in the hair of two newborns in the other report.[40] No information was available on the intake of the drugs by the mothers or the analyzed hair length.

Thieme and Sachs[59] published a report on a segmental hair analysis for clozapine using LC–MS/MS to examine the drug history of a multiple poisoning case of a woman. The segmentation was done in 3-cm segments and in very fine steps with segments of 1–2.5 mm steps on single hair for comparison.

The case of an 87-year-old man with suspicious behavior living in a retirement home was described by Kintz et al.[49] The segmental analysis of a 6-cm hair strand using LC–MS/MS revealed positive findings for promethazine although no information was available on a possible dosage.

Gaillard et al[16] reported the homicide of a 1-month-old baby that was confirmed by an exhumation of the body 8 months after the funeral. The lethal intoxication with cyamemazine of a sibling a few months later raised the awareness of the prosecutor and led to the investigation. The toxicological investigations showed the presence of amitriptyline and nortriptyline in the liver and cerebrospinal fluid and positive results for amitriptyline, nortriptyline, and bromazepam in a 3-cm hair strand using LC–MS/MS. Later the mother admitted to pouring 20 mL of drinkable amitriptyline solution (40 mg/mL) into the feeding bottle of the child, representing a total dose of 800 mg amitriptyline. It was hypothesized that the hair concentrations of amitriptyline and nortriptyline are related to the poisoning whereas bromazepam was probably taken by the mother during pregnancy.

Hair analysis results from patients under treatment with atomoxetine were presented by Papaseit et al.[38] They analyzed the hair samples in segments using LC–MS/MS and besides atomoxetine, sertraline concentrations were found in one hair sample and risperidone concentrations were found in the hair of two patients while the dosage was known.

Ricard et al[51] published a case report on a hospitalized and hallucinating person with chronic exposure to scopolamine- and atropine-containing plants. The report focused mainly on an LC–MS/MS method for the detection of scopolamine and atropine but mentioned positive results for levomepromazine and chlorpromazine detected in hair using a different method. None of these substances were prescribed to the patient.

Two case reports from a DFC with amitriptyline use were published by Chatterton et al.[20] The first report was about the analysis of hair strands from a young child who was involved in a kidnapping and false imprisonment by the mother and the partner. A segmental analysis of 1-cm segments using LC–MS/MS revealed positive results for amitriptyline, nortriptyline, and other drugs over the entire length of 20 cm. Although no information was available on the administered dose, the analysis demonstrated a repeated administration of the drugs over a longer period. The second report presented three cases of administration of prescribed drugs to a child with one of the cases involving amitriptyline.[18] A mother, who had a prescription for amitriptyline, was accused of administrating amitriptyline to her children (7 and 12 years old) over a 6-12-month period. A segmental LC–MS/MS analysis of the 6-cm-long hair strand of the 7-year-old victim showed concentrations of amitriptyline and its metabolite nortriptyline in each segment. It was concluded that the administration of the drugs had occurred more than once over a longer period.

Kintz et al[7] presented data on hair concentrations of the most encountered drugs in DFCs over a 10-year period in France. This list includes the antidepressant amitriptyline for which hair concentrations from three cases were presented: one case with a single exposure to 25 mg amitriptyline and two cases with a repeated intake without dosage information. Other cases with repeated exposure to fluoxetine, haloperidol, paroxetine, and levomepromazine were presented as well, but again without any information on the dose. In all cases, 2 cm of hair was analyzed using LC–MS/MS.

The poisoning of a baby and consecutive hospitalization was described by Allibe et al.[21] In that case the toxicological screening of the blood and urine revealed a high concentration of amitriptyline and its metabolite. Consequently, hair samples from the baby, the mother, and the father were analyzed using LC–MS/MS to evaluate if the incident happened once or repeatedly. The analysis of the parents showed negative results in a 5-cm-long hair strand of the father and a 22-cm-long hair strand of the mother. Exposure to amitriptyline could therefore be excluded for the mother for about 22 months covering the time of pregnancy. Two hair samples of the baby, one sample directly after the acute poisoning and one sample 5 weeks later, were analyzed as segments and showed homogeneous high concentrations of amitriptyline and its metabolite nortriptyline. This was interpreted as an external contamination through heavy sweating. The analysis of the second sample showed a different profile of concentrations and covered a period with some distance from the acute exposure. The results regarding different aspects such as contamination and axial diffusion were carefully interpreted. A repeated exposure to amitriptyline was assumed although a contamination could not be excluded.

Marchei et al[39] described the case of a 4-year-old boy who was hospitalized and treated for an accidental intoxication with the psychoactive drugs of his older brother. A hair analysis of the child was ordered because of a suspicion that the mother had chronically administered the drugs. A 12-cm-long hair strand was segmented and analyzed using LC–MS/MS. The analysis revealed concentrations of quetiapine and sertraline throughout the segments, which was interpreted as a repeated administration.

In a comprehensive investigation, Wang et al[28] presented the results of hair analysis of several DFCs in Denmark over an 8-year period. Hair concentrations of numerous substances, including the antidepressants citalopram, mirtazapine, sertraline, and venlafaxine, as well as the antipsychotics chlorprothixene, promethazine, and quetiapine and the stimulant methylphenidate, were presented. The hair length investigated varied largely among the cases, but there was a segmental hair analysis using LC–MS/MS wherever possible. Information on the dosage was not known for any of the drugs.

5 | CONTROLLED DOSE STUDIES

The perfect situation would be to know what concentration is found in hair at a certain exposure to a drug and to use this knowledge to comprehensively interpret the results of hair analysis. These publications allow the controlled research of relations between the intake of drugs and the actual hair concentration found. Although it is known that inter-individual differences in the concentration of drugs in hair make such correlations almost impossible,[4,60,61] several groups performed controlled dose studies and investigated dose-concentration relationship with divergent results. These studies provide comparable circumstances regarding dosage and hair length, and they usually include higher case numbers.

5.1 | Publications without a correlation of hair concentration and dosage

Among the earlier researchers, in 1995, Couper et al[11] investigated the presence of therapeutic drugs in postmortem hair samples using GC–MS and quantified the substances using HPLC-DAD. Hair samples from 21 postmortem cases revealed hair concentrations of amitriptyline, nortriptyline, doxepine, dothiepin, imipramine, mianserin, trimipramine, haloperidol, chlorpromazine, and thioridazine. The dosage was known for haloperidol, amitriptyline, and trimipramine. The hair length was not given except for three cases with segmented analysis that were discussed in detail.

Negrusz et al[25] presented the results of a repeated hair analysis of a patient under treatment with a fixed daily dose of doxepine. The samples were taken before the therapy had begun and some months after the therapy had ended. Concentrations of doxepine and its metabolite in 1-cm segments repeatedly taken from the same area of the head were obtained using a GC–MS method.

Weinmann et al[48] analyzed the hair of six psychiatric patients under treatment with clozapine, flupentixol, zuclopenthixol, haloperidol, and other neuroleptics using LC–MS/MS. A segment of 1–2-cm-long hair was analyzed, and the daily dose was known. Although flupentixol and zuclopenthixol were regularly administered, they were not found in the respective hair samples. Therefore, hair concentrations of clozapine, haloperidol, and other neuroleptics were presented.

Schneider et al[57] analyzed hair samples of three patients under fixed treatment with risperidone using an LC–MS/MS method. The segmental analysis provided data on hair concentrations of risperidone and the metabolite as well as metabolite-to-drug concentration ratios.

Wang et al[32] reported a segmental hair analysis of a patient with a known dosage history of citalopram and sertraline. A 16-cm-long hair was cut into 1-cm segments (and 2-cm segments toward the distal end) to adapt to the time periods of changing dose regiments. The LC–MS/MS analysis provided hair concentration of citalopram and sertraline along the length of the shaft, which did not agree with dosage history.

5.2 | Publications with a correlation of hair concentration and dosage

In the early 1990 Uematso et al[46] and Matsuno et al[47] investigated possible dose-concentration relationship for haloperidol in human hair. The hair samples of 40 patients with fixed doses of haloperidol over 4 months were analyzed using radioimmunoassay (RIA) in 1–2-cm-long segments.[46] In addition, from 20 patients a nail sample was analyzed, and a segmented analysis was done on the hair samples of 10 patients with a changing dose regimen. Plasma samples in steady state were also analyzed, and the results were correlated with the found hair concentration and dosage. The authors found a significant correlation between the hair concentration and the plasma concentration and the daily dosage. The concentrations in nail were generally lower compared with that in the hair samples, while there was no correlation between hair and nail concentration. However, the concentration in nail correlated with the daily dose. In the second study,[47] the hair samples from 59 patients who were compliant under treatment with fixed daily doses of haloperidol for over 4 months were analyzed for haloperidol and reduced haloperidol using HPLC with a coulochem detector. Like the other study, the hair of some patients with a changing dose regimen was analyzed in segments while plasma samples were also analyzed. Again, the authors found significant correlations between the hair concentration and steady-state plasma levels and the daily dose.

Tracqui et al[9] investigated hair concentrations from 30 psychiatric patients under treatment with amitriptyline for at least 2 months. The dose was known in each case, and 3 cm of hair was analyzed using GC–MS. A significant correlation was found between the hair concentration and the total administered dose of amitriptyline.

Sato et al[52] analyzed hair samples of 23 patients with fixed doses of chlorpromazine using HPLC with a coulochem detector. Eleven patients had a co-administration of haloperidol, and steady-state plasma samples were analyzed as well. Separately a segmental hair analysis was done for five patients with a changing dose regimen. The hair of five patients with grizzled hair was divided into the white hair and black hair sections and separately analyzed. The authors found positive significant correlations between the hair concentration and steady-state plasma concentration and daily dose. The co-administration of haloperidol did not affect the correlation. The concentration of chlorpromazine was found to be much lower in the white section of grizzled hair, indicating a strong melanin binding.

Pragst et al[13] comprehensively investigated hair samples of 56 psychiatric patients under stable treatment with the tricyclic antidepressants amitriptyline, nortriptyline, doxepine and its metabolite, maprotiline, and clomipramine and its metabolite. Three hair samples from different locations on the head were analyzed using GC–MS in 3-cm-long segments. The daily dose was known from self-reports. A significant correlation was not found between the hair concentration and daily dose. The authors also presented data on metabolite-to-drug ratios and discussed these results regarding the drug incorporation. They also correlated the hair concentrations with therapeutic plasma levels from the literature.

Clozapine dose-concentration relationship was also the focus of a study by Cirimele et al.[53] In this study hair, blood, and sweat samples of 26 schizophrenic patients under therapy for at least 4 months were analyzed using GC–MS and HPLC-DAD. In a segment of 3 cm of hair the authors found a significant correlation between the daily dose and the hair concentration.

Shen et al[14] described the hair analysis for antidepressants and neuroleptics using GC–MS from 35 psychiatric patients with known daily doses. The analysis of 2 cm hair from the proximal end provided data on amitriptyline, doxepine, chlorpromazine, chlorprothixene, trifluoperazine, clozapine, haloperidol, carbamazepine, and trihexylphenidyl in human hair. A significant correlation was found between the hair concentration and daily dose for chlorpromazine and clozapine.

Pigmentation effects and dose-hair concentration relationship were also investigated by Kronstrand et al[54] who analyzed hair and blood samples from 12 gray-haired patients under low-dose clozapine treatment. The white and black portions of 2–7-cm-long gray hair strands were separately analyzed using LC–MS/MS for clozapine and its metabolite (including metabolite-to-drug concentration ratios). Similar to Sato et al[52] the authors found higher concentrations in the black hair portion, which supports a strong melanin-binding for the incorporation of clozapine into hair. The hair concentrations also correlated with the dose in this study.

Sticht et al[41] analyzed hair samples of 17 children under treatment with methylphedinate using GC–MS. The dosage was known, and time of treatment as well as the hair lengths investigated varied among the cases. Only a low correlation between the hair concentration and dose was found for that collective, which, however, increased only when brown or black hair was involved in the correlation.

Binz et al[55] found no correlation between hair concentration and dose in the segmental analysis of 10 patients under treatment with quetiapine using LC–MS/MS. They also investigated the ratio of quetiapine and the metabolite. Generally lower 7-OH-quetiapine concentrations toward the distal end of the hair length lead to increasing ratios toward the distal end.

In a comprehensive study, Licata et al[23] presented the validation of an LC–MS/MS method for the detection of 50 psychoactive drugs and applied it to hair samples from 234 patients with headache and under treatment of different drugs. The dosage for at least 3 months before sampling was obtained from self-reports, and segments of 3-cm hair were analyzed. Hair concentrations and metabolite-to-drug ratios were presented for amitriptyline, clomipramine, citalopram, fluoxetine, sertraline, duloxetine, venlafaxine, mirtazapine, trazodone, levomepromazine, levosulpiride, quetiapine, and other pharmaceutical drugs. In a follow-up study on the data, Ferrari et al[62] correlated the cumulative doses and hair concentrations and found significant relationships for amitriptyline, citalopram, duloxetine, and venlafaxine.

Günther et al[44] presented chlorprothixene hair concentrations from a segmental LC–MS/MS analysis of 20 deceased psychiatric patients. The authors estimated the daily dosage using prescription records and pharmacy pickups and correlated it with the hair concentrations found. A significant positive correlation was found for chlorprothixene and its metabolite in the first 1-cm segments. Günther et al[56] also presented a similar approach for the detection of quetiapine and its metabolite in hair samples of 22 deceased psychiatric patients using LC–MS/MS. The dose was estimated using the pharmacy pickup data, and the hair samples were analyzed in segments. In contrast to the results of Binz et al[55] a significant correlation was found between the hair concentration and the estimated dose for quetiapine and its metabolite. In both studies, results from postmortem blood analysis were correlated with the hair concentrations in the first segment. However, a correlation was found only between hair concentration in the first segment and the postmortem blood for quetiapine.

Sun et al[58] focused on dose-hair concentration relationships for risperidone and its metabolite in a collective of 34 schizophrenic patients with a stable intake of a fixed daily dose for at least 3 months. The group analyzed 1-cm-long hair segments using LC–MS/MS. No correlation was found between the hair concentration and the daily dose. In addition, analyzed serum samples showed a significant correlation between the hair concentration and the serum concentration.

Recently, Wang et al[37] presented a comprehensive investigation on 46 patients under treatment with several antidepressants and neuroleptics. The hair samples were analyzed in 2-cm segments, and the fixed daily dose was known for all patients. An applied LC–MS/MS method for the detection of 23 analytes provided hair concentrations of amisulpride, aripiprazole and its metabolite, clozapine and its metabolite, chlorpromazine, paroxetine, risperidone and its metabolite, perphenazine, olanzapine and its metabolite, haloperidol, sulpiride, and sertraline and its metabolite. In accordance with Shen et al,[14] Kronstrand et al,[54] and Cirimele et al,[53] the authors found significant dose-hair concentration correlations for chlorpromazine and clozapine and its metabolite. However, the data did not suggest significant dose-hair concentration relationships for aripiprazole and its metabolite, olanzapine and its metabolite, risperidone and its metabolite, and perphenazine. The metabolite-to-drug ratio was also presented wherever possible.

5.3 | Analytical issues and interpretation issues

The aim of this review was not just to compare the methodology and analytical background but also to present the detected hair concentrations. However, some analytical issues must be addressed for the interpretation of such hair concentrations. Xiang et al[2] and Cuypers et al[61] outlined the analytical considerations for hair analysis and the caveats that arise for the interpretation of hair analysis results. The complex drug incorporation into hair has been extensively studied over the years and is well summarized by different fundamental books and reviews[1, 63] and will not be discussed in detail in this review. Known factors such as the physicochemical properties, hair color, sample preparation, and inter-subject variability directly influence the drug incorporation and thus the detectable concentration in hair.[1,63] Nowadays, sensitive methods such as LC–MS/MS and GC–MS are widely used for the detection of drugs at low concentrations in hair. Most of these methods were correctly validated according to national and international guidelines, but the detected concentrations can vary significantly due to different washing and extraction procedures. On the contrary, Saar et al[8] pointed out that some published methods do not have a consistent quality regarding validation criteria. The use of quality control samples and legislation of the laboratory accreditation gives some level of quality assurance and comparability. As quality control samples and calibration samples are prepared by spiking blank hair, fortifying blank hair, or using authentic decontaminated hair samples, there might be a bias in the validation itself.[2,61] Proficiency testing is highly recommended to achieve comparability among laboratories, but most proficiency tests with authentic hair samples do not include antidepressants and antipsychotics at all. Therefore, it is recommended for each laboratory to build its own database for the interpretation of hair concentrations with the limitation that these databases are suitable only for comparison and not for the estimation of a dosage history.[2] Kintz et al[60] and Cuypers et al[61] addressed the lack of a consensus for washing procedures as problematic because external contamination is a major risk for false-positive results. They laid out that the washing steps are indispensable to exclude external contamination as much as possible although other works suggest that a washing solvent inducing swelling of the hair is a possible way of incorporation from the hair surface into hair itself.[64] The discrimination of single or repeated exposure is an ongoing discussion in the literature and especially important in DFCs. Kintz et al[60] pointed out that results from a single segment of hair are not suitable for this discrimination and segmental analysis is required. Especially in young children it is impossible to distinguish between acute and chronic administrations as stated by Alvarez et al.[65] The fact that drug concentrations were also found in consecutive segments after a single

drug use[66] was explained by differences in hair growth, axial diffusion through the hair shaft, incorporation through sweat, external contamination, and cosmetic treatment. Kintz et al[67] later proposed that the segment corresponding to the time of the event should have three times higher concentrations than the surrounding segments. Kintz et al[60] and Cuypers et al[61] outlined and summarized the caveats for the interpretation of hair results and the importance of this knowledge. This helps investigators to critically interpret the results of hair analyses and avoid false assumptions.

6 | CONCLUSION

Many antidepressants and antipsychotics were developed and marketed over the past years. This review does not include all available substances but aimed to include the most prescribed substances at least in Germany.[6] The absence of some substances is, therefore, related to different relevance or marketing situations in other regions. Other substances might be outdated but can become relevant when old leftovers from prescriptions are used. However, in our opinion we could present a comprehensive overview although some readers might miss a substance.

Although there are guidelines from international associations like Society of Hair Testing (SoHT)[68] or the European Workplace Drug Testing Society (EWDTS),[69] the scientific outcome may vary largely regarding the presented hair lengths, hair color, or cosmetic treatment. The presented publications also varied largely regarding the validation protocol and sample preparation, which seems to have resulted from advancements made in the analytical techniques over the past 30 years. Most of the publications preferred GC–MS and LC–MS/MS techniques that allow the detection of low amounts of drugs and metabolites in hair. Other techniques were mostly used in older publications before the emergence of MS. Information on hair color or hair cosmetics was rarely included in the publications but is crucial for the comparative interpretation of drug concentrations in hair. In addition, usually results from scalp hair were presented. The mechanisms involved in implications from hair growth, pigmentation, type of hair, and cosmetic treatment were comprehensively described by other authors[1,63] and were not discussed in detail in this review. However, the results from different hair lengths are not comparable to another because they reflect a different time window. Even the controlled dose studies varied largely in that point between 1-cm-long segments and 3-cm-long segments. Methodology publications that only presented such hair concentrations as a proof of applicability seldom focus on this comparability and yet for some substances, they are the only source of data. A harmonization regarding the used hair length or a general agreement on the use of standardized hair lengths would be of great favor for comparability. The important pre-analytic steps such as extraction and decontamination were not compared for the purpose of this publication but also showed great variance between the publications.

The review showed that the detection of some antidepressants and antipsychotics in human hair has been researched very well while other substances do not have a well-founded database. Mirtazapine, for example, was widely prescribed in Germany in 2018[6] (183 million defined daily doses) but was rarely investigated by controlled dose studies to our knowledge. Licata et al[23] included only two patients under mirtazapine treatment with a self-reported dose. Other available publications were mostly methodology papers[15,19,27,28] without information on the prescribed dose or the duration of treatment. These publications describing method validation and application often presented a fixed set of substances of a certain context (drugs of abuse or pharmaceutical psychoactive substances or combinations of them) and their approach to achieve sensitive and comprehensive methods for further use. Therefore, they focused on optimal sample treatment and chromatography and other analytical issues but lacked reliable information on dose or treatment duration for the applied cases. However, these methods should be valuable when applied to larger studies on known doses. Case reports with a more profound background information are useful as they sometimes can reflect similar situations as the own casework, but the reviewed reports also vary in their use of hair length and information on dosage.

Comparable results were found for almost all substances except for clozapine, haloperidol, amitriptyline, nortriptyline, risperidone and its metabolite, methylphenidate, citalopram, chlorpromazine, chlorprothixene, and quetiapine. These substances were investigated in some controlled dose studies with higher case numbers. Some of these studies proved significant correlations between the dosage and the hair concentration, whereas other authors failed to find significant relationships. Even though such correlations sound promising, many authors suggested that they fail to give a valid estimation of the administered dose as the influence of inter-individual variations on drug incorporation is too strong.[4,37,60]

Comprehensive data on postmortem hair samples were rare for most of the reviewed substances. Postmortem hair samples are prone to over-interpretation and false assumption of long-term exposure to drugs because of possible external contamination from body fluids or environmental contamination.[70] Comparison with data from controlled dose studies from living individuals and interpretation of own results should be undertaken with great care. The authors want to encourage other groups to share their postmortem casework on the reviewed substances to increase data availability and understanding in this field.

There are many pitfalls in the interpretation of hair concentrations, as they cannot be easily used for comparison.[61] Still the summary and overview of the published concentration ranges provides valuable data and can help to give rough estimations about the history of drug exposure. Such knowledge can be crucial for the further investigation of a forensic case.

For many substances there were at least two or three publications describing hair concentrations, which is favorable but weakened by the fact that case numbers were very low for most substances. This lack of comparable case numbers results in a low statistical power and complicates the interpretation of own casework. Although the presence of great number of controlled dose studies on some substances is to be welcomed, there is clearly a lack of such work for the

other substances. The authors want to encourage other groups to fill this gap to help other investigators who might encounter a case where reliable data on hair concentrations of a certain substance are crucial. A greater part of the controlled dose studies was done in the 1990s and early 2000s after which research on controlled dose studies seemed to decrease. The more recent work of Sun et al,[58] Licata et al,[23] and Wang et al[37] is, therefore, a favorable development toward a better understanding and statistical base of concentrations of antidepressants and antipsychotics in human hair. Collaboration with medical stations where patients are treated with antidepressants and antipsychotics serves as a good base for retrospective dose studies with a proper ethical foundation. A better harmonization of used hair lengths and available case information such as hair color, hair treatment, and dosage is needed to improve the quality, database, and guidance for the interpretation of hair concentrations of antidepressants and antipsychotics within our scientific community.

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