Knowledge discovery from patient forums: gaining novel medical insights from patient experiences

Dirkson, A.R.

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APPENDICES

A

TECHNICAL DETAILS OF ADE EXTRACTION

In Appendix A, we will elaborate on the technical details of how we preprocessed our data (Section A.0.1), how we trained and evaluated models to extract adverse drug events (ADE) (Section A.0.2), how we trained and evaluated machine learning models to map ADEs to the medical ontology SNOMED-CT (Section A.0.3) and how we linked reported ADEs to the medication for which the patient reports them (Section A.0.4). The Python code is publicly available at `https://github.com/AnneDirkson/CHyMer`.

A.0.1. DATA PREPROCESSING

We preprocess the data with the pipeline described in Chapter 2 that includes replacing URLs and email addresses with the strings -URL- and -EMAIL- with regular expressions, lower-casing and tokenizing the text using NLTK, converting British to American English, expanding abbreviations to their full form (e.g., lol to laughing out loud) and expanding contractions (e.g., I"m to I am). Spelling mistakes were corrected using a combination of relative Levenshtein edit distance (i.e., how many insertions, deletions, and replacements are necessary to change one word into another word relative to the length of the word) and cosine similarity based on a static (or context independent) word2vec language model. A word2vec language model represents words based on how they are used, meaning that words used in similar contexts are closer together in the model and therefore have a lower cosine similarity. We excluded drug names in the FDA database of drugs[1] from spelling correction to prevent common drug names from replacing uncommon, similar drug names. Removing empty messages (567) and messages in a language other than English (1,493) left 121,516 messages. We also normalized drug names to their generic forms using the FDA database. We manually added experimental names before FDA approval for novel GIST drugs (BLU-285 for Avapritinib and DCC-2618 for Ripretinib).

[1] Downloaded from: `https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-data-files`

	F_1	Precision	Specificity	Sensitivity/Recall
Token level performance	0.626	0.723	0.995	0.553
Entity level performance	0.716	0.739	0.998	0.695

Table A.1: The performance of the ADE extraction model on the held-out test set. Here the entity-level performance is lenient: an entity is regarded as true positive if at least one token has been retrieved correctly.

A.0.2. EXTRACTING ADES FROM TEXT

The task of extracting words from a text that contain a certain concept (like an Adverse Drug Event) is called Named Entity Recognition. For Named Entity Recognition, entities are represented using the BIO scheme (B-Beginning, I-Inside and O-Outside). By default, this representation is not able to represent entities that overlap with other entities (e.g., hand and foot pain) or are split (eyes are feeling dry). These entities are termed discontinuous entities. We converted annotated data labels to the FuzzyBIO annotation scheme (described in Chapter 7) to deal with these entity types. Discontinuous entities are transformed into continuous sequences that the BIO scheme can handle by annotating the non-entity words in between.

We make use of a state-of-the-art machine learning model for named entity recognition (BERT [84]) that has been trained on a large data set of English medical social media (EnDR BERT [303]). BERT models are a type of transfer learning model. Transfer learning models reuse a model trained on one (usually larger) data set as a starting point for training a model on another (usually smaller) data set to perform a task such as named entity recognition. For our model, we experimented with BERT models trained on biomedical text (i.e., PubmedBERT [119], BioBERT [174], and SciBERT[28]), but they did not perform as well as EnDR BERT.

The initialization of such models is stochastic (i.e., has a degree of randomness). This can result in suboptimal models [336]. To reduce this effect and create a more robust model, we use an ensemble of 10 models trained with different initialization seeds (1, 2, 4, 8, 16, 32, 64, 128, 256 and 512) following Weissenbacher et al. [336] and Miftahutdinov and Tutubalina [206]. We split our labeled data into training (80%), a validation (penultimate most recent 10% of the data), and a test set (most recent 10% of the data). We added a second publicly available data set of patient forum texts labeled for ADEs (CADEC [151]) to the training set. We also tried using PsyTAR [353] to increase the amount of data, but this was not beneficial. For each of the 10 models, we train for 3 or 4 epochs based on the results of the model on the first validation data. We use a one-cycle learning rate (LR) policy (max LR of 5^{-5}) to train the models. We average the output of the 10 models using majority voting.

Table A.1 reports the performance of the extraction of ADEs from text. The metrics used to calculate performance are recall, precision, and the F_1 score. Recall is the percentage of true positives that have been found. Precision is the percentage of true positives among the retrieved instances. The F_1 score is a measure of the overall performance: it is the harmonic mean of precision and recall.

Here, tokens are relevant words that are part of an ADE. Our algorithm was able to retrieve 55.3% of all true positive tokens (“Recall”) in a held-out test set and 72.3% of

the retrieved tokens are true positives ("Precision"). An entity is another term for the full concept e.g., "pain in chest" is an entity while "pain", "in" and "chest" are the tokens belonging to the entity. Our algorithm was able to retrieve 52.3% of all entities fully and 16.6% partially. On average, 69.5% of all retrieved entities were true positives. With this performance, our model performs better than state-of-the-art models on this task [194, 337]. It still falls below human performance (average mutual $F_1 = 0.80$).

In addition to good performance, a model needs to be able to find entities that it has not seen in the training data [304]. We find that 40.2% of the true positive entities that our model finds are not present in the training data, indicating that our model is able to find novel entities in unlabeled data.

A.0.3. ADE NORMALIZATION

Normalization of adverse drug responses is the mapping of the text containing the ADE to concepts in an ontology (e.g., "cannot sleep" to Insomnia in SNOMED-CT). We use the current state-of-the-art method BioSyn [291] for normalizing the entities. We used the default parameters of BioSyn. BioSyn uses BioBERT [174] (a BERT model trained on biomedical text) to rank all possible concept labels for an extracted ADE. The highest ranking label is selected. As was done in Sung et al. [291], we split composite mentions to separate mentions using heuristic rules by D' Souza and Ng [70] (e.g., non-familial breast and ovarian cancers into non-familial breast cancer and ovarian cancers).

Our data does not contain annotations for normalization (i.e., the relevant concept IDs for each ADE mention). We rely on three publicly available data sets for training our normalization model: CADEC [151], PsyTAR [353] and the Clinical Findings subset of the COMETA corpus [20].

We choose a curated subset of SNOMED, the CORE Problem List Subset as our target ontology. We try to map the concepts in the data sets to synonymous concepts in the CORE subset if possible. We do so by checking for a direct mapping in the community-based mappings in BioPortal [220] between the original concept. We also map the concept to its parent if the parent is in the CORE (e.g., "moderate anxiety" to "anxiety"). As target concepts, we include all concepts of the CORE subset. SNOMED concepts present in the training data that could not be mapped to a CORE concept and SNOMED concepts present in the registration trial data that could not be mapped to a CORE concept as candidates. We also removed all concepts that are not in the Clinical Findings of SNOMED CT (e.g., procedures like knee replacement). This results in a total of 5813 concepts. To employ the BioSyn method, we need to collect all synonyms of the target SNOMED concepts. Synonyms for each concept are retrieved from the community based mappings in BioPortal [220] using the REST API and from the UMLS using pymedtermino [170].

The performance of the normalization model is shown in Table A.2. On average, the model could accurately label 64.5% of the ADEs when tested on a different data set than those on which the model was trained. For an additional 14.6% of the cases, the correct label was included in the top 5. We manually inspected these cases and found that 53 of 100 randomly selected cases, we would consider the first label to be correct or even better than the gold label. For example, the mention "severe abdominal pain" has the gold label "painful" (i.e., the label given by humans) and the predicted label "abdominal pain". Moreover, we inspected 100 random cases in which the correct label was not included in

Trained on	Tested on	Acc @1	Acc @5
CADEC & COMETA	PsyTAR	0.586	0.771
COMETA & PsyTAR	CADEC	0.663	0.807
CADEC & PsyTAR	COMETA	0.688	0.795
		0.645	**0.791**

Table A.2: The performance of our normalization model on a held-out data set. As the normalization model provides a ranking of candidate labels, Acc @1 and Acc @5 indicate the percentage of cases with the correct label in the top 1 and top 5, respectively. The bold numbers indicate mean values

Category	Frequency	Example
Correct concept	67	-
Extraction errors	22	“feet”, “nose”, “losing”
Predicted concept is related	6	“kidney issues” instead of “nephrosis”
No SNOMED equivalent	2	“comfy eyes, woozy face”
Wrong but no clear reason	2	

Table A.3: Manual analysis of 100 randomly selected found ADEs in the GIST data

the top 5 and found that for 36 of those we would consider the predicted label as correct. Thus, the performance in Table A.2 is likely an underestimation.

One concern is the propagation of errors in the pipeline (i.e., errors from extraction will influence normalization). Previous work has shown that ADE normalization is mainly hampered by errors made during extraction [337]. To evaluate the pipeline end-to-end, we manually inspect 100 of the ADEs found in the GIST data. As can be seen in Table A.3, we find that 67 of the 100 cases are correct, while 22 of the 100 are incorrect due to extraction errors prior to normalization. Thus, extraction appears to still be the major bottleneck.

Another concern is that the normalization model should be able to predict new types of ADEs that are absent in the training data. The BioSyn model should theoretically be able to do so because all the concepts of the SNOMED CT are considered as possible targets for mapping. Our normalization model is indeed able to predict classes that were not part of the training data at an Accuracy@1 of 0.417 on average and an Accuracy@5 of 0.612 on average for the external data sets. On our own GIST data, we also see empirically that 15.0% of the predicted concepts are not part of the training data.

Manual analysis of the predicted concepts in the GIST data revealed that some ADEs for tyrosine kinase inhibitors (TKIs) (e.g. split nails, hair color change, and hand-foot syndrome) were not included in the target concepts. We manually added 5 concepts and 2 synonyms to existing concepts to improve normalization.

A.0.4. LINKING ADES TO MEDICATION

First, we identify all drugs mentioned in each message using a dictionary based on the RxNORM [313]. During preprocessing, we already converted all brand names to their generic equivalents (e.g., Gleevec to Imatinib).

We use heuristic rules to determine which drug is linked to each ADE. Whenever possible, we select the drug mentioned prior to the ADE in the message. If there is

none, we select the drug mentioned after the ADE in the message. If there are no drugs mentioned in the message, we select the first drug mentioned in the conversational thread prior to the message. These rules were determined based on further manual annotation of our annotated subset by the first author. In some cases, it was not clear which drug the patient believed was causing the ADE and these cases were excluded. In this data set, our rules were 93% accurate if we restricted the possible drugs for linking to a predetermined list (Imatinib, Sunitinib, Regorafenib, Avapritinib, Ripretinib, Nilotinib, Pazopanib, Ponatinib, Sorafenib).

thread_id	post_id	word	tag
7581	155	I	O
7581	155	really	O
7581	155	do	O
7581	155	not	O
7581	155	know	O
7581	155	what	O
7581	155	I	O
7581	155	would	O
7581	155	do	O
7581	155	without	O
7581	155	you	O
7581	155	guys	O
7581	155	!!	O
7581	155	I	O
7581	155	started	O
7581	155	sunitinib	O
7581	155	12	O
7581	155	days	O
7581	155	ago	O
7581	155	and	O
7581	155	now	O
7581	155	have	O
7581	155	some	O
7581	155	crazy	O
7581	155	rash	B-ADR
7581	155	all	I-ADR
7581	155	over	I-ADR
7581	155	my	I-ADR
7581	155	chest	I-ADR
7581	155	and	I-ADR
7581	155	back	I-ADR
7581	155	.	O
7581	155	They	O
7581	155	are	O
7581	155	little	O
7581	155	red	B-ADR
7581	155	elevated	I-ADR
7581	155	bumps	I-ADR
7581	155	all	O
7581	155	over	O
7581	155	that	O
7581	155	itch	O
7581	155	.	O
7581	155	Has	O
7581	155	anyone	O
7581	155	else	O
7581	155	had	O

7581	155	this	O
7581	155	issue	O
7581	155	?	O
7581	156	My	O
7581	156	husband	O
7581	156	has	O
7581	156	it	O
7581	156	but	O
7581	156	not	O
7581	156	itchy	O
7581	156	and	O
7581	156	his	O
7581	156	is	O
7581	156	from	O
7581	156	imatinib	O
7581	157	"	O
7581	157	I	O
7581	157	did	O
7581	157	,	O
7581	157	it	O
7581	157	only	O
7581	157	showed	O
7581	157	up	O
7581	157	on	O
7581	157	my	O
7581	157	legs	O
7581	157	and	O
7581	157	but	O
7581	157	it	O
7581	157	did	O
7581	157	not	O
7581	157	itch	O
7581	157	.	O
7581	157	I	O
7581	157	went	O
7581	157	to	O
7581	157	the	O
7581	157	emergency	O
7581	157	room	O
7581	157	,	O
7581	157	just	O
7581	157	in	O
7581	157	case	O
7581	157	it	O
7581	157	was	O
7581	157	an	O
7581	157	allergic	O
7581	157	reaction	O
7581	157	,	O

7581	157	but	O
7581	157	it	O
7581	157	ended	O
7581	157	up	O
7581	157	being	O
7581	157	“	O
7581	157	nothing	O
7581	157	”.	O
7581	158	Yes	O
7581	158	I	O
7581	158	had	O
7581	158	some	O
7581	158	of	O
7581	158	that	O
7581	158	plus	O
7581	158	it	O
7581	158	dried	B-ADR
7581	158	out	I-ADR
7581	158	my	I-ADR
7581	158	hands	I-ADR
7581	158	and	I-ADR
7581	158	feet	I-ADR
7581	158	I	O
7581	158	fought	O
7581	158	that	O
7581	158	with	O
7581	158	immunotherapy	O
7581	158	by	O
7581	158	putting	O
7581	158	it	O
7581	158	on	O
7581	158	my	O
7581	158	feet	O
7581	158	then	O
7581	158	socks	O
7581	158	and	O
7581	158	put	O
7581	158	it	O
7581	158	on	O
7581	158	my	O
7581	158	hands	O
7581	158	with	O
7581	158	cotton	O
7581	158	gloves	O
7581	158	with	O
7581	158	the	O
7581	158	blue	O
7581	158	plastic	O
7581	158	gloves	O

7581	158	on	O
7581	158	top	O
7581	159	My	O
7581	159	mouth	B-ADR
7581	159	is	I-ADR
7581	159	constantly	I-ADR
7581	159	on	I-ADR
7581	159	fire	I-ADR
7581	159	too	O
7581	159	.	O
7581	159	Stuff	O
7581	159	that	O
7581	159	is	O
7581	159	not	O
7581	159	even	O
7581	159	spicy	O
7581	159	burns	O
7581	159	!!!	O
7581	159	I	O
7581	159	was	O
7581	159	just	O
7581	159	trying	O
7581	159	to	O
7581	159	eat	O
7581	159	some	O
7581	159	cheese	O
7581	159	Doritos	O
7581	159	with	O
7581	159	melted	O
7581	159	colby	O
7581	159	jack	O
7581	159	cheese	O
7581	159	on	O
7581	159	them	O
7581	159	and	O
7581	159	my	O
7581	159	mouth	O
7581	159	is	O
7581	159	on	O
7581	159	fire	O
7581	159	.	O
7581	159	My	O
7581	159	first	O
7581	159	9	O
7581	159	days	O
7581	159	on	O
7581	159	it	O
7581	159	were	O
7581	159	really	O

7581	159	good	O
7581	159	but	O
7581	159	I	O
7581	159	think	O
7581	159	the	O
7581	159	sunitinib	O
7581	159	side	O
7581	159	effects	O
7581	159	are	O
7581	159	way	O
7581	159	worse	O
7581	159	than	O
7581	159	imatinib	O
7581	159	!!	O
7581	160	"	O
7581	160	Yes	O
7581	160	I	O
7581	160	get	O
7581	160	rash	B-ADR
7581	160	on	I-ADR
7581	160	my	I-ADR
7581	160	neck	I-ADR
7581	160	and	I-ADR
7581	160	chest	I-ADR
7581	160	,	O
7581	160	some	O
7581	160	mornings	O
7581	160	I	O
7581	160	wake	O
7581	160	with	O
7581	160	eyes	B-ADR
7581	160	so	I-ADR
7581	160	swollen	I-ADR
7581	160	I	O
7581	160	can	O
7581	160	hardly	O
7581	160	see	O
7581	160	"	O
7581	161	Had	O
7581	161	rash	B-ADR
7581	161	and	O
7581	161	it	O
7581	161	took	O
7581	161	a	O
7581	161	bit	O
7581	161	for	O
7581	161	me	O
7581	161	to	O
7581	161	adjust	O

7581	161	to	O
7581	161	sunitinib	O
7581	161	-	O
7581	161	rash	O
7581	161	finally	O
7581	161	gone	O
7581	162	"	O
7581	162	My	O
7581	162	wife	O
7581	162	had	O
7581	162	similar	O
7581	162	issues	O
7581	162	when	O
7581	162	she	O
7581	162	initially	O
7581	162	started	O
7581	162	on	O
7581	162	imatinib	O
7581	162	,	O
7581	162	but	O
7581	162	went	O
7581	162	away	O
7581	162	after	O
7581	162	1	O
7581	162	.	O
7581	162	5	O
7581	162	weeks	O
7581	162	.	O
7581	162	What	O
7581	162	helped	O
7581	162	was	O
7581	162	that	O
7581	162	her	O
7581	162	oncologist	O
7581	162	prescribed	O
7581	162	some	O
7581	162	steroid	O
7581	162	,	O
7581	162	and	O
7581	162	also	O
7581	162	I	O
7581	162	had	O
7581	162	her	O
7581	162	taking	O
7581	162	Epsom	O
7581	162	Salt	O
7581	162	with	O
7581	162	Baking	O
7581	162	Powder	O

7581	162	baths	O
7581	162	.	O
7581	162	It	O
7581	162	helped	O
7581	162	pull	O
7581	162	toxins	O
7581	162	out	O
7581	162	of	O
7581	162	the	O
7581	162	skin	O
7581	162	and	O
7581	162	relieve	O
7581	162	itching	O
7581	162	and	O
7581	162	discomfort	O
7581	162	almost	O
7581	162	immediately	O
7581	162	.	O
7581	162	She	O
7581	162	took	O
7581	162	these	O
7581	162	baths	O
7581	162	x2	O
7581	162	per	O
7581	162	day	O
7581	162	."	O

Table A.4: Example annotation of NER data for ADE extraction

B

SUPPLEMENTARY FILES FOR CHAPTER 8

thread_id	post_id	word	tag	concept
5065	1873	"	O	-
5065	1873	On	O	-
5065	1873	day	O	-
5065	1873	4	O	-
5065	1873	of	O	-
5065	1873	imatinib	O	-
5065	1873	,	O	-
5065	1873	was	O	-
5065	1873	very	O	-
5065	1873	nauseous	B-ADR	-
5065	1873	all	O	-
5065	1873	day	O	-
5065	1873	.	O	-
5065	1873	Previous	O	-
5065	1873	days	O	-
5065	1873	I	O	-
5065	1873	had	O	-
5065	1873	taken	O	-
5065	1873	the	O	-
5065	1873	imatinib	O	-
5065	1873	with	O	-
5065	1873	yogurt	O	-
5065	1873	.	O	-
5065	1873	But	O	-
5065	1873	was	O	-
5065	1873	out	O	-
5065	1873	last	O	-
5065	1873	night	O	-
5065	1873	so	O	-
5065	1873	I	O	-
5065	1873	took	O	-
5065	1873	it	O	-
5065	1873	with	O	-
5065	1873	something	O	-
5065	1873	else	O	-
5065	1873	.	O	-
5065	1873	Going	O	-
5065	1873	to	O	-
5065	1873	try	O	-
5065	1873	yogurt	O	-
5065	1873	again	O	-
5065	1873	tonight	O	-
5065	1873	and	O	-
5065	1873	see	O	-
5065	1873	if	O	-
5065	1873	it	O	-
5065	1873	makes	O	-

5065	1873	a	O	-
5065	1873	difference	O	-
5065	1873	.	O	-
5065	1873	Only	O	-
5065	1873	other	O	-
5065	1873	side	O	-
5065	1873	effect	O	-
5065	1873	is	O	-
5065	1873	cold	B-ADR	-
5065	1873	hands	I-ADR	-
5065	1873	and	I-ADR	-
5065	1873	feet	I-ADR	-
5065	1873	while	O	-
5065	1873	the	O	-
5065	1873	rest	O	-
5065	1873	of	O	-
5065	1873	the	O	-
5065	1873	body	O	-
5065	1873	is	O	-
5065	1873	warm	O	-
5065	1873	.	O	-
5065	1873	These	O	-
5065	1873	side	O	-
5065	1873	effects	O	-
5065	1873	are	O	-
5065	1873	workable	O	-
5065	1873	!	O	-
5065	1873	Do	O	-
5065	1873	you	O	-
5065	1873	take	O	-
5065	1873	it	O	-
5065	1873	with	O	-
5065	1873	a	O	-
5065	1873	certain	O	-
5065	1873	food	O	-
5065	1873	every	O	-
5065	1873	night	O	-
5065	1873	?"	O	-
5065	1874	I	O	-
5065	1874	have	O	-
5065	1874	been	O	-
5065	1874	taking	O	-
5065	1874	mine	O	-
5065	1874	at	O	-
5065	1874	night	O	-
5065	1874	around	O	-
5065	1874	11pm	O	-
5065	1874	with	O	-
5065	1874	a	O	-

5065	1874	couple	O	-
5065	1874	cookies	O	-
5065	1874	and	O	-
5065	1874	a	O	-
5065	1874	large	O	-
5065	1874	glass	O	-
5065	1874	of	O	-
5065	1874	water	O	-
5065	1874	and	O	-
5065	1874	then	O	-
5065	1874	I	O	-
5065	1874	drink	O	-
5065	1874	a	O	-
5065	1874	bottle	O	-
5065	1874	of	O	-
5065	1874	ensure	O	-
5065	1874	after	O	-
5065	1874	it	O	-
5065	1874	.	O	-
5065	1874	It	O	-
5065	1874	seems	O	-
5065	1874	to	O	-
5065	1874	work	O	-
5065	1874	I	O	-
5065	1874	have	O	-
5065	1874	not	O	-
5065	1874	felt	O	-
5065	1874	nauseous	O	-
5065	1874	just	O	-
5065	1874	a	O	-
5065	1874	lot	O	-
5065	1874	of	O	-
5065	1874	tummy	O	-
5065	1874	rumbling	O	-
5065	1874	.	O	-
5065	1874	it	O	-
5065	1874	will	O	-
5065	1874	be	O	-
5065	1874	my	O	-
5065	1874	6th	O	-
5065	1874	day	O	-
5065	1874	tonight	O	-
5065	1875	Hey	O	-
5065	1875	NAME	O	-
5065	1875	...	O	-
5065	1875	I	O	-
5065	1875	take	O	-
5065	1875	mine	O	-
5065	1875	about	O	-

5065	1875	an	O	-
5065	1875	hour	O	-
5065	1875	before	O	-
5065	1875	bedtime	O	-
5065	1875	.	O	-
5065	1875	I	O	-
5065	1875	have	O	-
5065	1875	tried	O	-
5065	1875	numerous	O	-
5065	1875	things	O	-
5065	1875	to	O	-
5065	1875	see	O	-
5065	1875	which	O	-
5065	1875	works	O	-
5065	1875	best	O	-
5065	1875	.	O	-
5065	1875	I	O	-
5065	1875	am	O	-
5065	1875	now	O	-
5065	1875	taking	O	-
5065	1875	my	O	-
5065	1875	imatinib	O	-
5065	1875	with	O	-
5065	1875	a	O	-
5065	1875	glass	O	-
5065	1875	of	O	-
5065	1875	dark	B-STR	CS06033
5065	1875	chocolate	I-STR	CS06033
5065	1875	almond	I-STR	CS06033
5065	1875	milk	I-STR	CS06033
5065	1875	with	O	-
5065	1875	much	O	-
5065	1875	success	O	-
5065	1875	.	O	-
5065	1875	Dark	B-STR	CS05345
5065	1875	chocolate	I-STR	CS05345
5065	1875	also	O	-
5065	1875	helps	O	-
5065	1875	with	O	-
5065	1875	nausea	B-ADR	-
5065	1875	and	O	-
5065	1875	the	O	-
5065	1875	almond	O	-
5065	1875	milk	O	-
5065	1875	has	O	-
5065	1875	lots	O	-
5065	1875	do	O	-
5065	1875	health	O	-
5065	1875	benefits	O	-

5065	1875	.	O	-
5065	1875	I	O	-
5065	1875	try	O	-
5065	1875	to	O	-
5065	1875	stay	B-STR	CS03264
5065	1875	away	I-STR	CS03264
5065	1875	from	I-STR	CS03264
5065	1875	dairy	I-STR	CS03264
5065	1875	as	O	-
5065	1875	much	O	-
5065	1875	as	O	-
5065	1875	possible	O	-

Table B.1: Example of real annotated data for NER and entity linking of coping strategies.

thread_id	Text	Label*
5065	'" On day 4 of imatinib , was very **nauseous** all day . Previous days I had taken the imatinib with yogurt . But was out last night so I took it with something else . Going to try yogurt again tonight and see if it makes a difference . Only other side effect is cold hands and feet while the rest of the body is warm . These side effects are workable ! Do you take it with a certain food every night ?" ', 'I have been taking mine at night around 11pm with a couple cookies and a large glass of water and then I drink a bottle of ensure after it . It seems to work I have not felt nauseous just a lot of tummy rumbling . it will be my 6th day tonight ', 'Hey NAME ... I take mine about an hour before bedtime . I have tried numerous things to see which works best . I am now taking my imatinib with a glass of dark chocolate almond milk with much success . Dark chocolate also helps with **nausea** and the almond milk has lots do health benefits . I try to ***stay away from dairy*** as much as possible'	1
5065	'" On day 4 of imatinib , was very nauseous all day . Previous days I had taken the imatinib with yogurt . But was out last night so I took it with something else . Going to try yogurt again tonight and see if it makes a difference . Only other side effect is **cold hands and feet** while the rest of the body is warm . These side effects are workable ! Do you take it with a certain food every night ?" ', 'I have been taking mine at night around 11pm with a couple cookies and a large glass of water and then I drink a bottle of ensure after it . It seems to work I have not felt nauseous just a lot of tummy rumbling . it will be my 6th day tonight ', 'Hey NAME ... I take mine about an hour before bedtime . I have tried numerous things to see which works best . I am now taking my imatinib with a glass of dark chocolate almond milk with much success . Dark chocolate also helps with nausea and the almond milk has lots do health benefits . I try to ***stay away from dairy*** as much as possible'	0

5065	'" On day 4 of imatinib , was very **nauseous** all day . Previous days I had taken the imatinib with yogurt . But was out last night so I took it with something else . Going to try yogurt again tonight and see if it makes a difference . Only other side effect is cold hands and feet while the rest of the body is warm . These side effects are workable ! Do you take it with a certain food every night ?" ', 'I have been taking mine at night around 11pm with a couple cookies and a large glass of water and then I drink a bottle of ensure after it . It seems to work I have not felt nauseous just a lot of tummy rumbling . it will be my 6th day tonight ', 'Hey NAME ... I take mine about an hour before bedtime . I have tried numerous things to see which works best . I am now taking my imatinib with a glass of dark chocolate almond milk with much success . Dark chocolate also helps with **nausea** and the almond milk has lots do health benefits . I try to stay away from dairy as much as possible ', 'I take mine nightly after a full meal normally diner but if I take later I normally have a peanut butter sandwich and then my pill . Sometimes I will have a couple Heresy kisses after taking my pill have had little or no nausea since I started my imatinib almost 9 months ago . ', 'My husband has been taking 400 mg for 6 years . He started breaking it in 1 / 2 and ***taking one half in the morning after breakfast and the other half at night with dinner*** . That seems to have helped his **nausea**.'	1
5065	'" On day 4 of imatinib , was very nauseous all day . Previous days I had taken the imatinib with yogurt . But was out last night so I took it with something else . Going to try yogurt again tonight and see if it makes a difference . Only other side effect is **cold hands and feet** while the rest of the body is warm . These side effects are workable ! Do you take it with a certain food every night ?" ', 'I have been taking mine at night around 11pm with a couple cookies and a large glass of water and then I drink a bottle of ensure after it . It seems to work I have not felt nauseous just a lot of tummy rumbling . it will be my 6th day tonight ', 'Hey NAME ... I take mine about an hour before bedtime . I have tried numerous things to see which works best . I am now taking my imatinib with a glass of dark chocolate almond milk with much success . Dark chocolate also helps with nausea and the almond milk has lots do health benefits . I try to stay away from dairy as much as possible ', 'I take mine nightly after a full meal normally diner but if I take later I normally have a peanut butter sandwich and then my pill . Sometimes I will have a couple Heresy kisses after taking my pill have had little or no nausea since I started my imatinib almost 9 months ago . ', 'My husband has been taking 400 mg for 6 years . He started breaking it in 1 / 2 and ***taking one half in the morning after breakfast and the other half at night with dinner***. That seems to have helped his nausea .'	0

Table B.2: Example of real annotated data for CS-ADE relation extraction. *1 indicates true CS-ADE relation. **Bold** indicates the ADE mentions and ***bold italic*** indicates the coping strategy (CS).

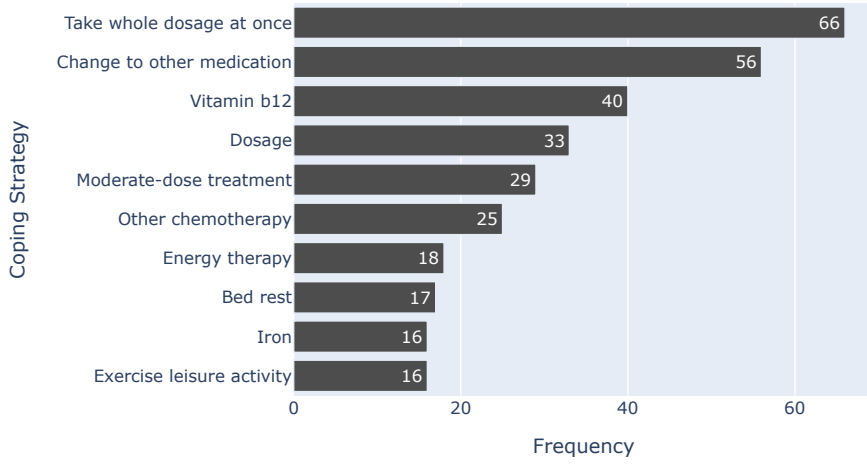

Figure B.1: **Top 10 coping strategies for Fatigue.** Manual examination of messages shows that patients recommend taking B12 or iron pills as a supplement. They also recommend naps ("bed rest"). Energy therapy appears to be a false positive and concerns messages about energy levels. Strategies regarding dosage ("Dosage", "Change to other medication", "Take whole dosage at once", "Moderate-dose treatment", "Other chemotherapy") do not appear to be about fatigue although they do relate to dosage.

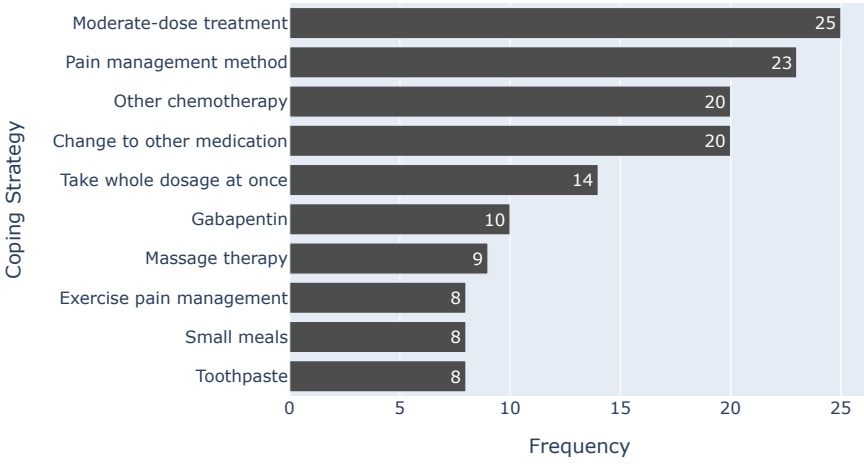

Figure B.2: **Top 10 coping strategies for Pain.** Manual examination of messages shows that patients recommend reducing the dosage of the primary medication ("moderate-dose treatment"), using gabapentin ("Gabapentin") or other pain medication ("Pain management method"), getting a massage ("massage therapy") or exercising ("Exercise pain management"). Small meals and toothpaste do concern messages around these topics but do not appear to be about pain management. Other categories related to dosage ("Other chemotherapy", "Take whole dosage at once") are not insightful.

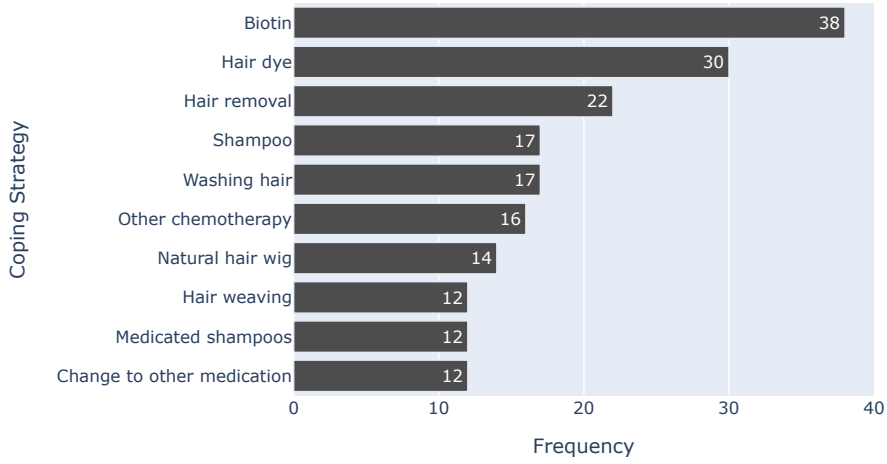

Figure B.3: **Top 10 coping strategies for Alopecia (hair loss).** Manual examination of messages reveals several true positives: Patients recommend using Biotin, using special shampoos, washing one's hair less, and wearing a wig. Other categories (e.g. "Hair dye", "Hair removal" and "Hair weaving") are false positives. The category "Hair dye" specifically mainly concerns messages where patients relay that their hair color has changed due to medication.

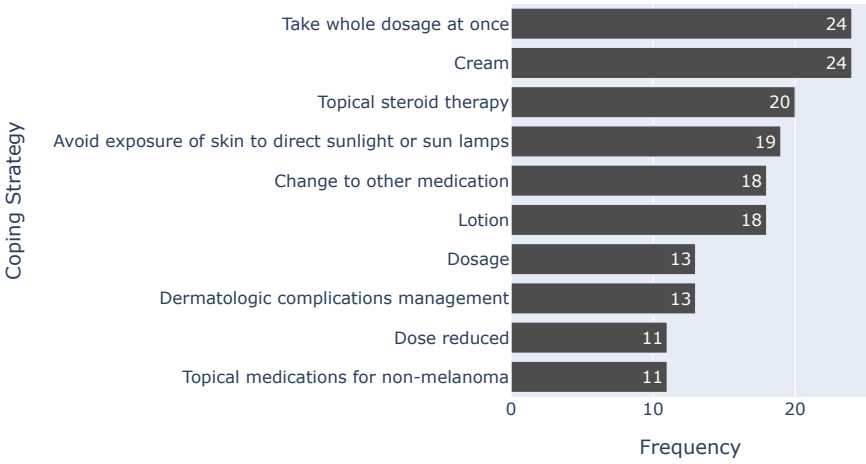

Figure B.4: **Top 10 coping strategies for Eruption (Rash).** Manual examination of messages shows that patients recommend cream, lotion, steroid creams, seeing a dermatologist, staying out of the sun and using sunscreen. The category "taking whole dosage at once" mainly contains the advice to the contrary i.e. split the dosage

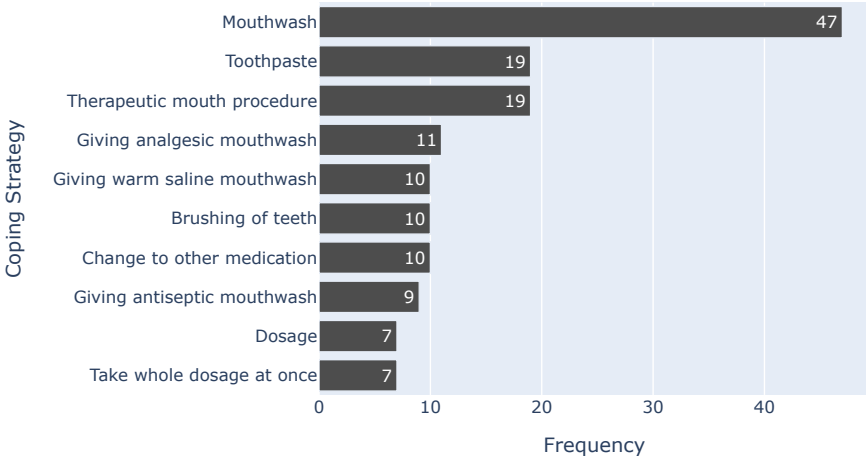

Figure B.5: **Top 10 coping strategies for a painful mouth.** Manual analysis of the messages relating to these coping strategies showed that patients recommend certain mouthwashes (e.g. magic mouthwash), using or avoiding certain toothpastes, and rinsing with saline water.

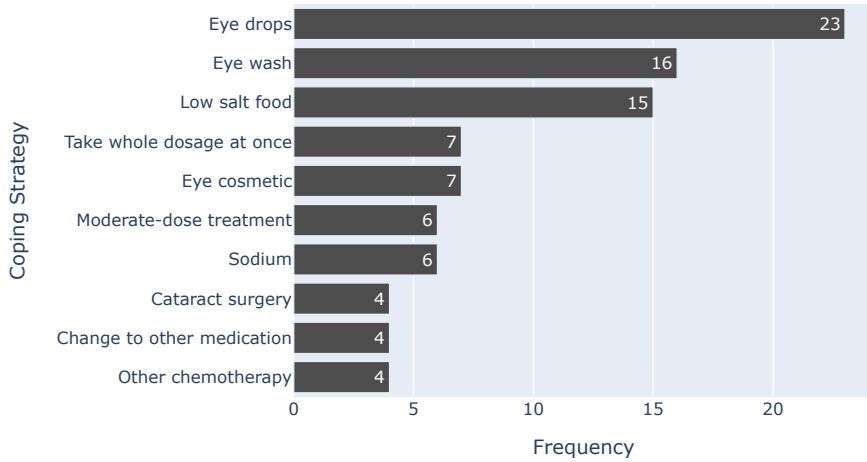

Figure B.6: **Top 10 coping strategies for Periorbital Edema.** Manual examination of messages shows patients recommend certain eye products including eye drops, or eye washes. They also discuss home remedies like cucumber and cotton pads with chamomile for on the eyes. Low salt food is also recommended.

C

SUPPLEMENTARY TABLES FOR CHAPTER 10

	Sunitinib (n=6)	Regorafenib (n=6)	Ripretinib (n=3)
Age (mean ± SD (range))	74.4 ± 8.0 (64-86)	65.5 ± 4.3 (60-71)	64.9 ± 4.6 (60-69)
Time since diagnosis in years (mean ± SD (range))	6.0 ±2.1 (3.8-9.4)	5.8 ± 1.8 (3.8 – 8.2)	3.4 ± 1.2 (2.1-4.6)
Sex			
– Male	2 (33.3%)	5 (83.3%)	2 (66.7%)
– Female	4 (66.7%)	1 (16.7%)	1 (33.3%)
Highest formal education			
– Primary school only	0	1 (16.7%)	0
– High school	1 (16.7%)	2 (33.3%)	0
– College or university	5 (83.3%)	3 (50%)	3 (100%)
Relationship status			
– Single	0	0	0
– Married/relationship	4 (66.7%)	5 (83.3%)	3 (100%)
– Separated/divorced	0	0	0
– Widowed	2 (33.3%)	1 (16.7%)	0
Comorbidities			
– None	2 (33.3%)	3 (50%)	1 (33.3%)
– One	1 (16.7%)	2 (33.3%)	1 (33.3%)
– Two or more	3 (50%)	1 (16.7%)	1 (33.3%)

Table C.1: Patient characteristics from the survey study for different tyrosine kinase inhibitors than imatinib

	Sunitinib (n=6)	Regorafenib (n=6)	Ripretinib (n=3)
Symptoms	Prevalence (%)	Prevalence (%)	Prevalence (%)
Swelling of the face or around the eyes	3 (50)	2 (33)	0 (0)
Swelling in any part of the body	1 (18)	1 (18)	0 (0)
Muscle aches, pains, or cramps	4 (67)	4 (67)	3 (100)
Aches or pains in joints	4 (67)	2 (33)	1 (33)
Food and drink tasting different from usual	5 (83)	4 (67)	0 (0)
Pain or soreness in mouth	5 (83)	2 (33)	0 (0)
Indigestion or heartburn	5 (83)	1 (18)	1 (33)
Skin problems (e.g. itchy skin, dry skin, skin discoloration)	5 (83)	4 (67)	2 (67)
Hand-foot syndrome	3 (50)	3 (50)	0 (0)
Problems because of changed appearance	2 (33)	0 (0)	3 (100)
Feeling confused	1 (18)	1 (18)	0 (0)
Trouble speaking	2 (33)	1 (18)	0 (0)
Auditory hallucinations	0 (0)	0 (0)	0 (0)
Visual hallucinations	1 (18)	0 (0)	0 (0)
Shortness of breath	1 (18)	4 (67)	1 (33)
Pain	4 (67)	3 (50)	2 (67)
Feeling weak	5 (83)	4 (67)	1 (33)
Appetite loss	4 (67)	2 (33)	1 (33)
Nausea	5 (83)	1 (18)	0 (0)
Vomiting	2 (33)	1 (18)	0 (0)
Constipation	3 (50)	1 (18)	2 (67)
Diarrhea	4 (67)	2 (33)	1 (33)
Fatigue	6 (100)	5 (83)	3 (100)
Problems with concentrating	3 (50)	1 (18)	1 (33)
Problems with remembering things	3 (50)	2 (33)	1 (33)

Table C.2: Prevalence scores for symptoms in the survey study for different tyrosine kinase inhibitors (TKI) than imatinib. Prevalence is based on percentage of patients with this symptom out of the total number of patients taking each TKI.

	Sunitinib (n=6)	Regorafenib (n=6)	Ripretinib (n=3)
Symptoms	Prevalence (%)	Prevalence (%)	Prevalence (%)
Fatigue	184 (8.0)	117 (9.5)	40 (12.6)
Nausea	111 (4.8)	35 (2.8)	14 (4.4)
Cramp	32 (1.4)	30 (2.4)	14 (4.4)
Disorder of skin	59 (2.6)	36 (2.9)	12 (3.8)
Edema	-	-	-
Pain[a]	92 (4.0)	80 (6.5)	13 (4.1)
Alopecia	90 (3.9)	72 (5.8)	42 (13.4)
Altered bowel function[b]	121 (5.2)	42 (3.4)	5 (1.6)
Pain in limb[c]	137 (5.9)	87 (7.1)	13 (4.1)
Facial swelling	-	-	-
Painful mouth	142 (6.1%)	27 (2.2)	-
Weight loss	20 (0.9)	38 (3.1)	6 (1.9)
Hand-foot syndrome	27 (1.2)	58 (4.7)	10 (3.1)
Hypertensive disorder	86 (3.8)	-	26 (2.1)
Taste sense altered	77 (3.3)	-	-

Table C.3: Prevalence scores for symptoms in the forum study for different tyrosine kinase inhibitors (TKI) than imatinib. Forum data was adapted from `https://dashboard-gist-adr.herokuapp.com/` accessed on July 14, 2021. Prevalence is based on the percentages of each symptom out of the total number of symptoms for each TKI were calculated. [a]includes: chronic pain and generalized aches and pains [b]includes: constipation and diarrhea [c]includes: any pain in upper or lower limb, excludes: cramp, muscle pain, hand-foot syndrome

Rank	Survey	Rank	Forum
1.	Fatigue	1.	Fatigue
2.	Pain or soreness in mouth*	2.	Painful mouth
	Indigestion or heart burn*	3.	Pain in limb
	Skin problems *	4.	Altered bowel function
	Nausea*	5.	Nausea
	Food and drink tasting different than usual*	6.	Pain
	Feeling weak*	7.	Alopecia
8.	Muscle aches, pains or cramps #	8.	Hypertensive disorder
	Aches and pains in joints#	9.	Taste sense altered
	Pain#	10.	Disorder of skin
	Appetite loss #		
	Diarrhea#		

Table C.4: Ranking of prevalence of symptoms related to sunitinib in survey study and forum study. * same prevalence (83%) # same prevalence (67%)

Rank	Survey	Rank	Forum
1.	Fatigue	1.	Fatigue
2.	Muscle aches, pains or cramps*	2.	Pain in limb
	Shortness of breath*	3.	Pain
	Skin problems *	4.	Alopecia
	Feeling weak*	5.	Hand-foot syndrome
	Food and drink tasting different from usual*	6.	Altered bowel function
7.	Hand-foot syndrome#	7.	Weight loss
	Pain #	8.	Disorder of skin
9.	†	9.	Nausea
		10.	Cramp

Table C.5: Ranking of prevalence of symptoms related to regorafenib in survey study and forum study. * same prevalence (67%) # same prevalence (50%) † six symptoms with same prevalence (33%)

CURRICULUM VITÆ

Anne DIRKSON

2022–present	Scientist Netherlands Forensics Institute
2018–2022	PhD. Computer Science Leiden Institute of Advanced Computer Science Universiteit Leiden
2016–2017	Junior Teaching Fellow University College Maastricht
2014–2016	MSc Neuroscience Vrije Universiteit Amsterdam
2011–2014	BA Liberal Arts & Sciences University College Maastricht
2005–2011	Secondary education (Bilingual VWO) Stedelijk College Eindhoven

LIST OF PUBLICATIONS

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6. Gautam Kishari, **Anne Dirkson** & Tim Majchrzak (2020). *An Exploratory Study of COVID-19 Misinformation on Twitter.* Online Social Networks and Media.

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3. **Anne Dirkson**, Suzan Verberne & Wessel Kraaij (2019), *Lexical Normalization of User-Generated Medical Text: Association for Computational Linguistics.* Proceedings of the Fourth Social Media Mining for Health Applications (SMM4H) Workshop & Task. Association for Computational Linguistics. 11-20.

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